Serevent Dossier

This information is provided in response to your request for information about Serevent® Diskus® (salmeterol xinafoate inhalation powder).

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In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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1. Change Summary

-Updated 2008 WAC prices. Added SMART Pediatric subanalysis. Updated GSK meta-analysis of serious asthma related outcomes for adults and pediatrics from the data presented at the FDA Dec 2008 Ad Com

2. EXECUTIVE SUMMARY

DISEASE: CONSENSUS TREATMENT GUIDELINES

Asthma: The National Asthma Education and Prevention Program (NAEPP) asthma management guidelines recommend the addition of a long-acting beta$_2$-agonist (LABA) to an inhaled corticosteroid (ICS) as one of the preferred treatments for patients ≥ 5 years of age with moderate to severe persistent asthma who are new to controller therapy. [1] A LABA plus an ICS is also recommended as one of the preferred treatments in patients whose asthma is no longer controlled by low-dose ICS alone.

Chronic Obstructive Pulmonary Disease (COPD): The GOLD Guidelines recommend 1) inhaled long-acting bronchodilator therapy in patients with a forced expiratory volume in 1 second (FEV_1) <80% predicted, and 2) the addition of an ICS to long-acting bronchodilator therapy in chronic obstructive pulmonary disease (COPD) patients with a post-bronchodilator FEV_1 of <50% predicted and a history of repeated exacerbations. [2] The ATS/ERS guidelines state that data from trials using concomitant LABA plus an ICS shows a significant additional effect on pulmonary function compared with the individual components alone and using different medication classes is a way of delivering treatment to obtain better results including improved lung function. [3]

BENEFITS OF *SEREVENT DISKUS* IN ASTHMA

• *Serevent Diskus* contains the LABA, salmeterol xinafoate, in a convenient *Diskus* device with a built-in dose counter. [4]

• *Serevent Diskus* is approved for use in children 4 years of age and older with asthma and was evaluated in over 2,500 children 4 to 11 years old, including 346 children treated for 1 year. [4]

• *Serevent Diskus* is approved for prevention of exercise-induced bronchospasm (EIB) in patients 4 years of age and older. [4]

• *Serevent Diskus* provided clinically significant improvements in FEV_1 (≥ 15%) on Day 1, which lasted 12 hours. Median time to onset post first-dose ranged from 30 to 48 minutes with maximum improvement within 3 hours. [4]

• *Serevent Diskus* has demonstrated efficacy for up to 1 year in adults, adolescents and children 4 years of age and older. [4]

• Salmeterol xinafoate, administered via inhalation aerosol, in combination with an ICS provided significantly greater improvements in lung function, symptom scores, and rescue albuterol use compared to double-dose ICS. [4]

• *Serevent Diskus* provided significantly greater improvements in pulmonary function, asthma symptoms, and patient satisfaction than montelukast when added to current ICS therapy in patients 12 years of age and older. [5]

BENEFITS OF *SEREVENT DISKUS* IN COPD

• *Serevent Diskus* provided significant improvements in pulmonary function on Day 1 (FEV_1 ≥ 12% and at least 200 mL) which lasted 12 hours. Significant improvements were noted at 2 hours post first-dose, which were maintained throughout 24 weeks of treatment. The mean time post-dose to peak bronchodilator effect ranged from 3.27 to 4.75 hours. [4]

• *Serevent Diskus* was designed to provide consistent dose delivery via the *Diskus* device at a flow rate of 60 L/min for 2 seconds. Studies have shown that the mean peak inspiratory flow (PIF) through a *Diskus* was 82.4 L/min in adult patients with obstructive lung disease and severely compromised lung function (FEV_1 20% to 30% of predicted). [4]

EFFICACY IN ASTHMA

• In two 12-week, pivotal trials, *Serevent Diskus* provided a significant, rapid, and well-maintained improvement in lung function without evidence of tachyphylaxis to the bronchodilator effects and without

increasing asthma exacerbation rates compared with “as needed” albuterol in adult and adolescent patients with asthma. (4) (6)

• In two 12-week, pivotal trials, *Serevent Diskus* provided significant improvement in lung function, asthma symptom scores, and rescue albuterol use compared with placebo in children 4 to 11 years old with asthma. (4) (7)

• In 4 pivotal trials, single-doses of *Serevent Diskus* prevented EIB when inhaled 30 minutes prior to exercise in adults, adolescents and children 4 to 11 years old. For many patients, this protective effect against EIB was still apparent up to 8.5 hours after a single dose. (4) (8) (9) (10)

EFFICACY IN COPD

• In 2 pivotal trials, *Serevent Diskus* provided greater improvements in pulmonary function endpoints compared with placebo in patients with chronic bronchitis with airflow limitation, with or without emphysema. Significant improvements in secondary endpoints assessing COPD symptoms were not seen. (4) (11)

SAFETY

• **BOXED WARNING:** Long acting $beta_2$-adrenergic agonists, such as salmeterol, the active ingredient in *Serevent Diskus*, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, *Serevent Diskus* should only be used as additional therapy for patients not adequately controlled on other asthma controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including *Serevent Diskus*. Data from a large placebo-controlled US study that compared the safety of salmeterol (Serevent® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). (4) (12)

• The data from the Salmeterol Multicenter Asthma Research Trial (SMART) are not adequate to determine whether concurrent use of ICSs or other asthma-controller therapy modifies the risk of asthma-related death. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by LABAs. (4)

• It is important to watch for signs of worsening asthma, such as increasing use of inhaled, short-acting $beta_2$-agonists (SABAs) or a significant decrease in peak expiratory flow (PEF) or lung function. Such findings require immediate evaluation. (4)

• *Serevent Diskus* should not be used to treat acute symptoms. (4)

• *Serevent Diskus* should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition. (4)

• *Serevent Diskus* is not a substitute for inhaled or oral corticosteroids. Corticosteroids should not be stopped or reduced when *Serevent Diskus* is initiated. (4)

• The most common adverse events ≥ 5%) reported in asthma clinical trials with *Serevent Diskus* (and placebo) in patients ≥ 12 years of age were: headache 13% (9%), nasal/sinus congestion 9% (6%), tracheitis/bronchitis 7% (4%), rhinitis 5% (4%), and influenza 5% (2%). (4)

• The most common adverse events (≥ 5%) reported in asthma clinical trials with *Serevent Diskus* (and placebo) in patients 4 to 11 years of age were: headache 17% (14%) and pharyngitis 6% (3%). (4)

• The most common adverse events (≥ 5%) reported in COPD clinical trials with *Serevent Diskus* (and placebo) were: headache 14% (11%), musculoskeletal pain 12% (10%), throat irritation 7% (6%), and cough 5% (4%). (4)

INDICATIONS

• **Asthma:** *Serevent Diskus* is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma. LABAs, such as salmeterol, the active ingredient in *Serevent Diskus*, may increase the risk of

asthma- related death. Therefore, when treating patients with asthma, *Serevent Diskus* should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose ICSs) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including *Serevent Diskus*. It is not indicated for patients whose asthma can be managed by occasional use of inhaled SABAs or for patients whose asthma can be successfully managed by ICSs or other controller medications along with occasional use of inhaled SABAs. (4)

• **Prevention of Exercise-Induced Bronchospasm:** *Serevent Diskus* is also indicated for prevention of EIB in patients 4 years of age and older. (4)

• **COPD:** *Serevent Diskus* is indicated for the long-term, twice-daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with COPD (including emphysema and chronic bronchitis). (4)

DOSING

• **Asthma:** For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). It is not indicated for patients whose asthma can be managed by occasional use of inhaled SABAs or for patients whose asthma can be successfully managed by ICSs or other controller medications along with occasional use of inhaled SABAs. If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period between doses, an inhaled SABA should be taken for immediate relief. (4)

• **COPD:** For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). (4)

• **Prevention of EIB:** One inhalation of *Serevent Diskus* at least 30 minutes before exercise has been shown to protect patients against EIB. When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and up to 12 hours in patients 4 to 11 years of age. Additional doses of salmeterol should not be used for 12 hours after the administration of this drug. Patients who are receiving *Serevent Diskus* twice daily should not use additional salmeterol for prevention of EIB. If regular, twice daily dosing is not effective in preventing EIB, other appropriate therapy for EIB should be considered. (4)

3. DISEASE DESCRIPTION

3.1 Asthma

Asthma: Epidemiology and Risk Factors

Asthma is one of the most common chronic diseases in the United States. According to the American Lung Association's Trends in Asthma Morbidity and Mortality report, approximately 22.9 million Americans (6.8 million children) had asthma in 2006.(13) In addition, 12.4 million people, or 54% of the people who had asthma at the time of the survey, had experienced an asthma attack in the previous year. Health care use in 2005 included 488,594 asthma-related hospitalizations and approximately 1.8 million emergency department visits. Deaths from asthma in 2005 numbered 3,884.(14) The economic cost of asthma in 2005 was estimated at $19.7 billion.(13)

Atopy, the genetic susceptibility for the development of an IgE-mediated response to environmental allergens, is the strongest identifiable predisposing factor for developing asthma.(1)

Asthma: Pathophysiology

Asthma is a chronic disease of bronchoconstriction, inflammation and remodeling of the airways.(1) In asthma, airway narrowing and subsequent airflow limitation lead to the symptoms of asthma. In an acute exacerbation, contraction of the bronchial smooth muscle, or bronchoconstriction, occurs in response to exposure to an inhaled allergen or irritant. The inflammatory reaction to an inhaled allergen involves a

complex interaction of a variety of cells, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, smooth muscle cells, and epithelial cells. As inflammation becomes more progressive and the disease becomes more persistent, factors such as edema, inflammation, mucus hypersecretion, and hypertrophy and hyperplasia of the airway smooth muscle lead to further airflow obstruction. In addition, airway inflammation results in an increase in the existing airway hyperresponsiveness. Over time, permanent structural changes may occur which result in loss of lung function that may be only partially reversible with therapy, also known as airway remodeling. Some of the structural changes which may occur include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and secretion. The interaction between symptoms, airway obstruction, bronchial hyperresponsiveness, and inflammation determines the clinical manifestations and severity of asthma as well as the response to treatment.

Asthma: Clinical Presentation

Patients with asthma have recurrent episodes of cough (particularly worse at night), wheezing, difficulty breathing, and chest tightness.[1] These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. Patients also experience bronchial hyperresponsiveness to various triggers. On physical examination, patients may exhibit hyperexpansion of the thorax (especially in children), use of accessory muscles, hunched shoulders, and chest deformity. Wheezing may occur during normal breathing or during a prolonged phase of forced exhalation, although wheezing may be absent between exacerbations. Patients may have increased nasal secretion, mucosal swelling and nasal polyps. In addition, atopic dermatitis/eczema or any other allergic skin condition may be present. Symptoms may be absent during the time of examination; therefore, a history of symptoms is important.

Asthma: National Asthma Education and Prevention Program Guidelines

The 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma recommend to first assess severity in newly diagnosed patients to determine initial therapy for patients with asthma.[1] For patients who have been receiving long-term controller medications, the guidelines recommend regular assessments of asthma control for monitoring and adjusting therapy. The guidelines provide impairment and risk criteria to assess both asthma severity and asthma control for each of the three age ranges: 0-4 years of age, 5-11 years of age, and ≥12 years of age. Impairment is defined as the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced. Risk is defined as the likelihood of either asthma exacerbations, progressive decline in lung function, or risk of adverse effects from a medication. In addition, the guidelines also recognize the use of validated assessment tools, like the Asthma Control Test and Childhood Asthma Control Test, to assess asthma control.

For each age range, there are six treatment steps which provide preferred, and for some steps alternative, treatment recommendations for both intermittent and persistent types of asthma. All patients, regardless if they have intermittent or persistent asthma, should receive a short-acting $beta_2$-agonist for quick relief of their asthma symptoms. Inhaled corticosteroids, either alone or in combination with other controller medications, continue to be the preferred first-line therapy for children and adults with persistent asthma. The guidelines also recommend the use of a long-acting beta-agonist (LABA) and an inhaled corticosteroid (ICS) as a preferred therapy for patients ≥5 years of age whose asthma is uncontrolled on their current controller and for patients ≥12 years of age with moderate to severe persistent asthma who are new to controller therapy.

3.2 Chronic Obstructive Pulmonary Disease (COPD)

COPD: Epidemiology and Relevant Risk Factors

Risk factors for COPD include cigarette smoking, environmental pollutants, and genetic factors such as α-$_1$ antitrypsin deficiency. Cigarette smoking accounts for approximately 90% of all COPD cases.[3] Smokers who are diagnosed with COPD have a rate of decline in forced expiratory volume in one second (FEV_1) that is 2 to 3 times that of non-smokers.[15]

According to the World Health Organization, by 2020 COPD will rise from the 12th to the 5th most prevalent disease and from the 6th to the 3rd most common cause of death worldwide.[16] The COPD in America Survey found that patients underestimated their symptom severity and overestimated their degree of disease control, which may lead to suboptimal disease management and a lower quality of life than necessary.[17]

COPD is a leading cause of morbidity and mortality and results in an economic and social burden that is both substantial and increasing.[18] COPD is often associated with acute exacerbations of symptoms that range from increased dyspnea and increased productive cough to acute respiratory failure. Reports suggest that patients experience exacerbations regularly (e.g., median rates of 2.4 and 3 episodes per year).[19,20] Hospital mortality of patients admitted for an acute exacerbation of COPD is approximately 10%.[21,22] Also, the long-term outcome is poor with mortality reaching 40% in one year.[21,23] A study evaluating 1,016 patients who were hospitalized for acute exacerbations showed that those who survived the first hospitalization had a 50% rate of rehospitalization within 6 months after discharge.[21] The direct and indirect costs of COPD to the U.S. in 2007 were estimated to be about $42.6 billion.[24]

COPD: Pathophysiology

COPD is a disease state characterized by airflow limitation that is not fully reversible.[3,18] The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The term COPD was introduced because chronic bronchitis and emphysema often coexist. It may, therefore, be difficult in an individual case to determine which is the major condition. Chronic bronchitis is defined as the presence of cough and sputum production for at least 3 months in each of two consecutive years. Emphysema, or destruction of the alveoli, is a pathological term that describes one of several structural abnormalities present in patients with COPD.

The chronic inflammation of COPD exists throughout the airways and parenchyma.[18] The intensity and cellular and molecular characteristics of the inflammation vary as the disease progresses. Over time, inflammation damages the lungs and leads to the pathologic changes characteristic of COPD. Key inflammatory cells include neutrophils, macrophages, and CD8+ T-lymphocytes.[25] There may also be an increase in eosinophils in some patients, particularly during exacerbations. Activated inflammatory cells in COPD release a variety of mediators, notably leukotriene B_4 (LTB_4), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α), and are thought to damage lung structures and/or sustain neutrophilic inflammation. In addition to inflammation, an imbalance of proteases and antiproteases in the lung and oxidative stress are two important pathogenic processes. These processes may themselves be consequences of inflammation, or they may arise from environmental or genetic factors. The lung has natural defense mechanisms, but genetic traits (e.g., alpha-1 antitrypsin deficiency), exposure to other environmental risk factors (e.g., infection, atmospheric pollution), the chronic nature of the inflammation, or the repeated nature of the injury may cause the irreversible breakdown of defenses.

COPD: Clinical Presentation

Throughout the course of the disease, physiological changes develop : mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale.[25] Initially, cough may be intermittent, but often becomes persistent or present every day. Chronic sputum production may also indicate COPD. Breathlessness or dyspnea is often considered the hallmark symptom of COPD and is often persistent (present every day) and progressive (worsens over time). Dyspnea is the symptom that causes most patients to seek medical attention, and is a major cause of disability and anxiety associated with the disease. Wheezing and chest tightness may also be present.

COPD: Approaches to Treatment-Principle Options/Practice Patterns

The increase in awareness and development of treatment recommendations for COPD to decrease morbidity and mortality are important goals of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines, initiated by the U.S. National Heart, Lung, and Blood Institute and the World Health Organization.[25] According to the GOLD guidelines, patients who have dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors should be tested for airflow limitation. For the diagnosis and assessment of COPD, spirometry is the standard of care. An $FEV_1/FVC < 0.70$ and

a post-bronchodilator FEV_1<80% of predicted confirms the presence of airflow limitation that is not fully reversible.

The GOLD Guidelines recommend long-acting inhaled bronchodilator therapy in those patients with FEV_1 <80% predicted and recognize that long-acting inhaled bronchodilators are more effective and convenient.[25] The GOLD Guidelines also recommend the addition of an inhaled corticosteroid (ICS) to long-acting inhaled bronchodilator therapy in COPD patients with a postbronchodilator FEV_1 of <50% predicted and a history of repeated exacerbations. Regular treatment with an ICS reduces the frequency of exacerbations and improves health status.

Table 1. Therapy at Each Stage of COPD[18]

Stage	Characteristics	Recommended Treatment
I: Mild COPD	FEV_1/FVC <0.70 FEV_1 ≥80% predicted	Active reduction of risk factors; influenza vaccination Add: Short-acting bronchodilator when needed
II: Moderate COPD	FEV_1/FVC <0.70 50%≤ FEV_1 <80% predicted	Add: Regular treatment with one or more long-acting bronchodilators Rehabilitation
III: Severe COPD	FEV_1/FVC <0.70 30%≤FEV_1 <50% predicted	Add: Inhaled corticosteroids if repeated exacerbations
IV: Very Severe COPD	FEV_1/FVC <0.70 FEV_1 <30% predicted or FEV_1 < 50% plus chronic respiratory failure	Add: Long-term oxygen therapy if respiratory failure Consider surgical treatments

3.3 Exercise-induced Bronchospasm (EIB)

EIB: Definition and Epidemiology

Exercise-induced bronchospasm (EIB) or exercise-induced asthma (EIA) is defined as a transient increase in airway resistance resulting from participation in strenuous physical activity. [26] In terms of lung function, EIB is characterized by a decrease in forced expiratory volume in 1 second (FEV_1) by at least ten percent. The prevalence of EIB varies from approximately 5% to 20% in the general population and 30% to 70% among elite athletes. [27] In patients with persistent asthma, the prevalence is at least 90%. Among sufferers of allergic rhinitis, the prevalence is estimated to be about 40%. [26]

EIB: Pathophysiology

EIB is a bronchospastic event caused by loss of heat, water, or both from the lungs during exercise because of hyperventilation of air that is cooler and dryer than that of the respiratory tree. [1] Some studies also suggest that the release of inflammatory mediators may be involved in the etiology of EIB.

EIB: Clinical Presentation

Asthma attacks precipitated by exercise are no different than attacks brought on by other stimuli. Patients experience wheezing, coughing, dyspnea, and chest tightness, in conjunction with airflow limitation and hyperinflation. Because children and young adults engage in more frequent physical activity, EIB is more commonly seen in these age groups. In EIB, the airways undergo dilation during physical activity which is followed by increasing obstruction beginning once the physical activity stops. Patients will show signs of airway obstruction within five to ten minutes after strenuous physical activity, which in most cases, reverses after twenty to thirty minutes. There are many factors which influence the severity of an attack including a patient's baseline airway reactivity, level of physical activity, and climate.

EIB: Approaches to Treatment

The most appropriate treatment for EIB is prophylaxis. Asthmatic patients can lessen the severity of attacks by engaging in a warm-up period prior to physical activity. Pharmacologic therapy depends upon the presentation of the disease. If EIB is present in an otherwise asymptomatic patient, there is no need for regularly scheduled medications. However, these patients should be monitored regularly to ensure they have no symptoms of asthma or reductions in peak expiratory flow in the absence of exercise because EIB is often a marker of inadequate asthma control. [1] Treatment of choice in a patient with EIB only consists of inhalation therapy with beta-agonists as needed immediately prior to physical activity. Cromolyn, nedocromil or leukotriene modifiers may also be useful for some patients.

If EIB is only one part of the asthmatic symptomatology, daily pharmacologic therapy is warranted. These patients require anti-inflammatory and bronchodilating medications to help control acute asthmatic symptoms.

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

GENERIC NAME: salmeterol xinafoate inhalation powder

BRAND NAME: SEREVENT® DISKUS®

THERAPEUTIC CLASS: Long-acting beta$_2$-adrenergic bronchodilator for inhalation

4.2 Dosage Forms, Package Sizes, NDC, WAC

Table 2. DOSAGE FORMS / NDC / WHOLESALE ACQUISITION COST

Dosage Strength	Description	Package Size	NDC	WAC*
Salmeterol xinafoate 50 mcg	Disposable, teal green device (DISKUS) packaged within a teal green, plastic-coated, moisture-protective foil pouch	60 blisters	0173-0521-00	$132.86
Salmeterol xinafoate 50 mcg	Institutional pack of 1 teal green, disposable device (DISKUS) packaged within a teal green, plastic-coated, moisture-protective foil pouch	28 blisters	0173-0520-00	$82.35
*WAC = wholesale acquisition cost effective as of 9/3/2008. WAC is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge-backs.				
Store at controlled room temperature, 20°-25°C (68°-77°F), in a dry place away from direct heat or sunlight. Keep out of reach of children. The *Diskus* is not reusable. *Serevent Diskus* should be discarded 6 weeks after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first. Do not attempt to take the *Diskus* apart.				

4.3 AHFS or Other Drug Classification

DPS/AHFS DRUG CLASSIFICATION: 12:12.08.08 selective beta$_2$-adrenergic agonist

4.4 FDA Approved Indications

Asthma and Exercise-Induced Bronchospasm (EIB) Indications: see Prescribing Information

Approval dates (Asthma): 9/19/1997 (12 years and older); 9/25/1998 (Children: 4 to 11 years old)

Approval date (EIB): 9/25/98 (4 years and older)

Chronic Obstructive Pulmonary Disease (COPD) Indication: see Prescribing Information

Approval date (COPD): 3/22/2002

4.5 Use in Special Populations

Refer to Enclosed Prescribing Information.

4.6 Pharmacology

Background

Salmeterol is a long-acting, highly selective, beta$_2$-adrenergic receptor agonist with bronchodilator and mast cell stabilizing properties, useful in the treatment of obstructive airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). (4) The pharmacologic effects of salmeterol, like other beta-agonists, are, at least in part, attributable to stimulation of intracellular adenyl cyclase and subsequent conversion of adenosine triphosphate (ATP) to cyclic 3',5'-adenosine monophosphate (cAMP). Increased intracellular cAMP concentrations are associated with bronchodilation and mast cell stabilization. Salmeterol has also exhibited several nonbronchodilator effects including anti-inflammatory effects. (28) (29) (30)

Animal Pharmacology

The salmeterol molecule was designed to overcome the short duration of action associated with earlier beta-agonists. Modification of the albuterol molecule to include a long, flexible, lipophilic side-chain or "tail" was theorized to anchor the drug in a lipophilic region near the active receptor site known as an "exosite". (31) Salmeterol is >10,000 times more lipophilic than albuterol. The introduction of an oxygen atom into the side-chain is thought to give the molecule flexibility, allowing it to hinge around the oxygen atom.

Persistent binding to the exosite is thought to permit the active moiety to remain in the region of the receptor and repeatedly engage and disengage the active receptor site. In isolated guinea-pig trachea and human bronchus, aerosolized salmeterol caused dose-related bronchodilation that persisted in excess of 7 hours independent of concentration. (31) The smooth muscle relaxant effect of salmeterol was readily reversed with a specific beta-receptor antagonist, sotalol, but reappeared within 90 minutes of removal of the antagonist from the tissue bath solution, confirming the sustained presence of the salmeterol molecule.

The constant presence of a drug at a receptor is generally thought to cause receptor down-regulation, resulting in tachyphylaxis or tolerance. Bronchodilator tachyphylaxis, however, has not been documented with salmeterol. The repeated engaging and disengaging of the receptor is thought to explain the lack of tachyphylaxis or tolerance observed with salmeterol. Since beta$_2$-receptors are located throughout smooth muscle of the bronchi and some receptors may be engaged while others are disengaged, the bronchodilating effect of salmeterol is a function of the net sum of engaged receptors. The length of time a receptor is engaged is unknown. In addition, ex-vivo studies in patients with asthma have shown that salmeterol occupies approximately 4% of available beta$_2$-receptors in the lung when administered at clinical doses. (32) The fact that salmeterol does not saturate all possible beta$_2$-receptor binding sites as well as the high affinity binding of the lipophilic side chain and reversible interaction with the active receptor site may explain the clinical utility of short-acting beta$_2$-agonists in reversing acute bronchospasm in clinical trials when patients are concurrently receiving salmeterol.

Potency

The lipophilic side chain of salmeterol may be responsible for the slightly longer onset of action associated with the drug when compared with short-acting beta$_2$-agonists (10-35 minutes versus 1-3 minutes, respectively). Salmeterol partitions into the outer phospholipid monolayer and then diffuses laterally through the cell membrane to engage the active receptor site. (31) It may also orient in a preferred stereochemical conformation to accommodate binding both exosite and active site.

The molecular conformation of salmeterol also appears to confer a high degree of potency at the beta$_2$-receptor and greater selectivity for beta$_2$- versus beta$_1$-adrenergic receptors relative to other beta$_2$-agonists. The beta$_2$-receptor binding affinity of salmeterol is approximately 50 times that of albuterol and salmeterol does not readily dissociate from the binding region in the cell membrane. (33) Salmeterol is approximately 15 times as potent as albuterol at beta$_2$-adrenergic receptors in vitro but 10,000 times

weaker than isoproterenol at $beta_1$-adrenergic receptors. [34] The relative potency and selectivity of five beta-agonists are described below.

Table 3. Comparative Potency and Selectivity of Five Beta-Agonists [34]

Agonist	Airway Potency ($ß_2$ receptors)	Cardiac Potency ($ß_1$ receptors)	Selectivity Ratio ($ß_2$:$ß_1$)
Isoproterenol	1	1	1
Albuterol	0.55	0.0004	1,375
Fenoterol	0.6	0.005	120
Formoterol	20	0.05	400
Salmeterol	8.5	0.0001	85,000

Although $beta_2$- adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenergic receptors are the predominant receptors in the heart, there are also $beta_2$ adrenergic receptors in the human heart comprising 10% to 50% of the total beta adrenoceptors. [4] The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

Non-Bronchodilator Effects

In addition to effects on bronchial smooth muscle, both *in vitro* and *in vivo* experimentation suggest that salmeterol may have non-bronchodilator, inhibitory effects on inflammatory processes associated with asthma and COPD. [28] These include inhibition of mediator release (such as histamine, leukotrienes, and prostaglandin D_2) from human lung, inhibition of inflammatory cell infiltration, eosinophil activation and degranulation. [4] [29] [30] [35] [36] [37] [38] Furthermore, a reduction in antigen-induced increases in vascular permeability, an increase in neutrophil apoptosis, and protection of the respiratory epithelium against effects of the bacteria *Pseudomonas aeruginosa* and *Haemophilus influenza* have been seen with salmeterol. [39] [40] [41] In addition to the anti-inflammatory effects, salmeterol has been associated with an increase in mucociliary clearance and ciliary beat frequency *in vitro*. [42] Additional studies are needed to define the role of salmeterol in inflammation.

Human Clinical Pharmacology

Salmeterol plasma concentrations of 0.1-0.2 mcg/L are seen in healthy volunteers 5-15 minutes following inhalation of a single 50 mcg dose of salmeterol, probably due to oral absorption of swallowed drug. Salmeterol is 94%-98% protein bound and extensively metabolized by hydroxylation with subsequent predominantly fecal elimination. The elimination half-life of salmeterol following oral administration is approximately 5.5 hours and no accumulation is seen with repeated doses in blood or tissue. [4] [31]

Ullman and Svedmyr [43] compared clinical effects of single doses of salmeterol 50, 100, and 200 mcg with albuterol 200 mcg in eight patients with asthma in a randomized, double-blind, crossover trial. All three doses of salmeterol produced mean peak increases in forced expiratory volume at one second (FEV_1) of 500-800 ml and mean peak increases in peak expiratory flow (PEF) of 71-100 L/min, which was similar to that caused by albuterol (500 ml and 74 L/min, respectively). There were no statistically significant differences in the time of onset of any of the doses, but, unlike albuterol, all three doses of salmeterol produced bronchodilation that persisted throughout the 12-hour study period. The authors concluded that salmeterol 50 or 100 mcg is approximately equivalent to albuterol 200 mcg in bronchodilating activity.

4.7 Pharmacokinetics/Pharmacodynamics

Refer to Enclosed Prescribing Information.

4.8 Contraindications

Refer to Enclosed Prescribing Information.

4.9 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.10 Adverse Events

Refer to Enclosed Prescribing Information.

4.11 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.12 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.13 Dosing and Administration

Refer to Enclosed Prescribing Information.

4.14 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

5. EFFICACY AND SAFETY TRIALS (FDA APPROVED)

5.1 Pivotal Safety and Efficacy Trials in Patients with Asthma

Adults and Adolescents

In two large, randomized, double-blind studies, *Serevent Diskus* 50 mcg BID was compared with albuterol inhalation aerosol 180 mcg four times a day (QID) and placebo in adolescent and adult patients with mild to moderate asthma (protocol defined as 50% to 80% predicted forced expiratory volume in 1 second [FEV_1], actual mean of 67.7% at baseline), including patients who did and who did not receive concurrent inhaled corticosteroids. (4) (6) The efficacy of *Serevent Diskus* was demonstrated over the 12-week period with no change in effectiveness over this time period. There were no gender- or age-related differences in safety or efficacy. There was no development of tachyphylaxis to the bronchodilator effect of salmeterol noted in these studies. The median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) ranged from 30 to 48 minutes after a 50 mcg dose of *Serevent Diskus*. Maximum improvement in FEV_1 generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients. Treatment with *Serevent Diskus* resulted in significant improvements in peak expiratory flow (PEF) and asthma symptoms (Table 4).

Table 4. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data) (4)

Efficacy	Time	Placebo	*Serevent*	Albuterol
Randomized subjects, n		152	149	148
Mean AM peak expiratory flow rate (L/min)	Baseline	394	395	394
	12 weeks	396	427*	394
Mean % days with no asthma symptoms	Baseline	14	13	12
	12 weeks	20	33	21
Mean % nights with no awakenings	Baseline	70	63	68
	12 weeks	73	85*	71
Rescue medications (mean no. of inhalations per day)	Baseline	4.2	4.3	4.3
	12 weeks	3.3	1.6†	2.2
Asthma exacerbations		14%	15%	16%
*$P < 0.001$ vs. Placebo and albuterol; †$P < 0.001$ vs. Placebo				

Table 5 below summarizes the adverse events that occurred at a frequency ≥3% in the group receiving *Serevent* and were more common than in the placebo group.

Table 5. Adverse Events in Two 12-Week Asthma Trials (Combined Data)(4)

Adverse Event	Placebo N=152	*Serevent* 50 mcg BID N=149	Albuterol 180 mcg QID N=150
Nasal/sinus congestion, pallor	6%	9%	8%
Rhinitis	4%	5%	4%
Headache	9%	13%	12%
Asthma	1%	3%	<1%
Tracheitis/bronchitis	4%	7%	3%
Influenza	2%	5%	5%

Pediatrics

Two pivotal U.S. 12-week, double-blind, placebo-controlled, parallel-group, multicenter studies evaluated the efficacy of chronic dosing with salmeterol powder in pediatric patients (ages 4-11 years) with mild to moderate asthma. In one study of 449 patients, salmeterol 25 mcg and 50 mcg administered twice daily via the *Diskus* and albuterol 200 mcg (via Rotahaler®) administered four times daily were compared with placebo. (4) Patients were permitted to continue inhaled steroids, nedocromil sodium and/or cromolyn sodium provided the dose remained constant throughout the study. The use of other beta-agonists or theophylline was prohibited.

The efficacy of salmeterol inhalation powder was demonstrated over the 12-week treatment period with respect to periodic serial PEF (36% to 39% postdose increase from baseline) and FEV_1 (32% to 33% postdose increase from baseline). (4) Salmeterol was effective in demographic subgroup analyses (gender and age) and was effective when coadministered with other inhaled asthma medications such as short-acting bronchodilators and inhaled corticosteroids.

In the second study of 207 patients, salmeterol 50 mcg (via Diskhaler®) twice daily was compared with placebo. (7) On treatment day 1 and at week 12, the weighted mean percent predicted PEF and weighted mean FEV_1 were significantly higher ($P \leq 0.008$) at all time points evaluated over the 12-hour post-dosing period in patients treated with salmeterol powder compared with placebo. Supplemental albuterol use declined from baseline in both groups, but the mean reduction from baseline was significantly greater in the salmeterol group (0.8 ± 0.2 puffs/day) versus the placebo group (0.3 ± 0.1 puffs/day) ($P = 0.004$). During the 12 weeks of treatment, the percentage of nights with no awakenings increased 9.1% for salmeterol-treated patients and 4.1% for placebo-treated patients (not significant). There were no significant between-group differences for drug-related adverse events. Four percent of salmeterol-treated patients and 6% of placebo-treated patients experienced adverse events judged by the investigators to be related to the study medication.

Table 6 below summarizes the adverse events that occurred at a frequency ≥3% in the group receiving *Serevent* and were more common than in the placebo group.

Table 6. Adverse Events in Two 12-Week Pediatric Asthma Trials (Combined Data)(4)

Adverse Event	Placebo N=215	*Serevent* 50 mcg BID N=211	Albuterol 200 mcg QID N=115
Ear signs and symptoms	3%	4%	9%
Pharyngitis	3%	6%	3%
Headache	14%	17%	20%
Asthma	2%	4%	<1%
Skin rashes	3%	4%	2%
Urticaria	0	3%	2%

5.2 Pivotal Safety and Efficacy Trials in COPD

Two pivotal, randomized, double-blind, double-dummy, placebo-controlled, parallel group, 24-week studies were conducted to assess the efficacy of salmeterol via the *Diskus* device in 702 patients with COPD. (44) (45) (46) (47) The studies included treatment arms for Advair Diskus® (fluticasone propionate and salmeterol inhalation powder) and fluticasone propionate, but only the arms including salmeterol will be reported here.

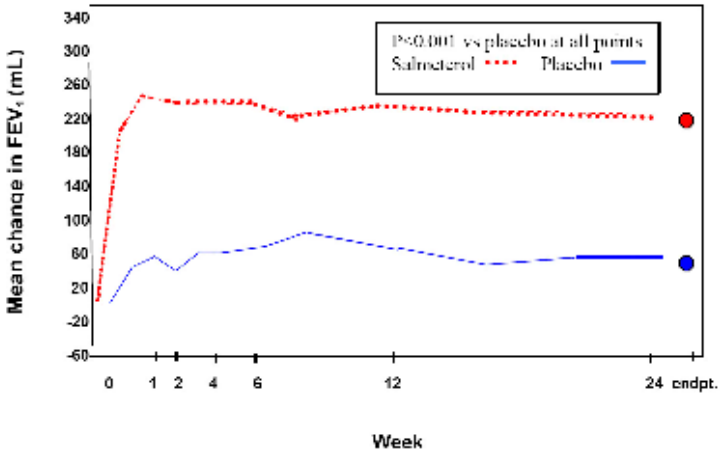
Patients were required to have a FEV_1/FVC ratio <70% and a FEV_1<65% of predicted but >0.70L **or** a FEV_1 ≤0.70L but >40% of predicted. Patients also had to achieve a score of ≥ 2 on the Modified Medical Research Council (MMRC) Dyspnea Scale and a score of ≥4 on the Chronic Bronchitis Symptoms Questionnaire (CBSQ). During the trials, all concurrent use of inhaled/oral corticosteroids and bronchodilators was discontinued. Theophylline was permitted if the dose had been stable for at least 1 month. Albuterol was provided as rescue medication. Assessments were made at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24. Patients who experienced an exacerbation could be treated with antibiotic therapy as an outpatient for two exacerbations. Patients were withdrawn from the study if a third exacerbation occurred, if oral/inhaled corticosteroids were required or if the patient was hospitalized.

The primary efficacy measures were the mean change from baseline in pre-dose FEV_1 and 2-hour post-dose FEV_1. Other efficacy measures were Chronic Bronchitis Symptoms Questionnaire (CBSQ), Transition Dyspnea Index (TDI), Chronic Respiratory Disease Questionnaire (CRDQ), incidence and time to first exacerbation, time to study withdrawal, morning PEF, and daytime/nighttime albuterol use. In addition, onset and duration of action were analyzed. Results are listed below.

Mean Change from Baseline at Endpoint of Two-Hour Post-Dose FEV_1

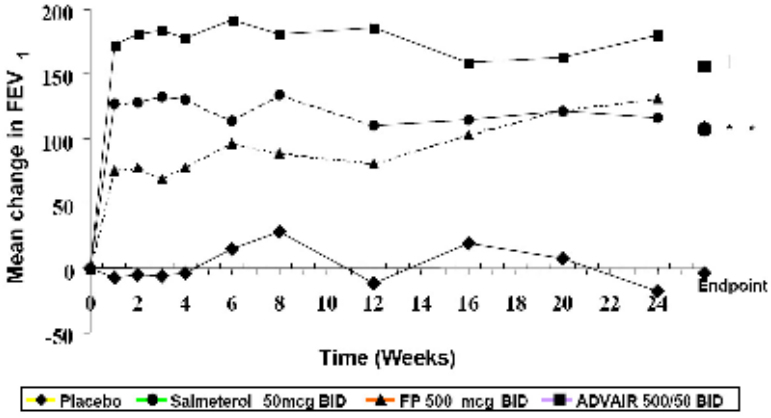
Salmeterol was more effective compared with placebo in increasing 2-hour post-dose FEV_1 at endpoint (seeTable 7). Salmeterol had a rapid onset (Day 1, $P<0.001$) and had sustained improvement in FEV_1 indicating a lack of tolerance after 24 weeks of treatment (see Figure 1). Also, improvements in FEV_1 greater than 150 mL were maintained for at least 12 hours, supporting twice-daily dosing.

Figure 1. Mean Change from Baseline for 2-Hour Post-Dose FEV_1 – Integrated Data (ITT) from Studies 1 and 2 (48)



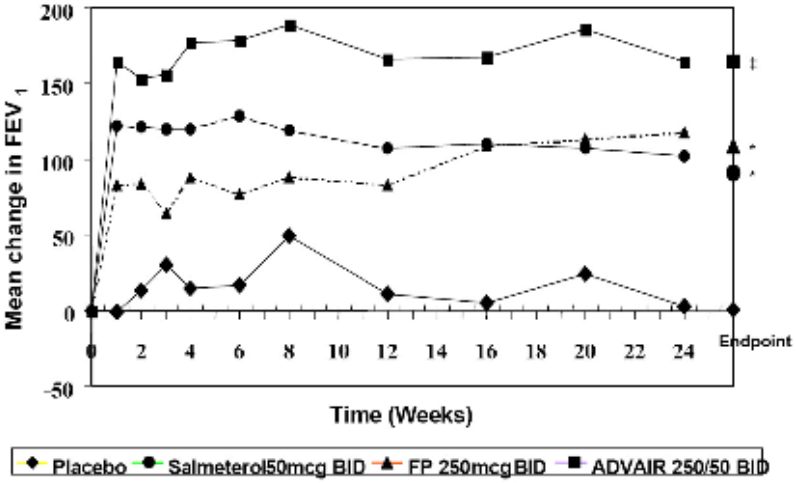
In Study 1 (Figure 2) and Study 2 (Figure 3), treatment with salmeterol 50 mcg provided significant improvements in pre-dose FEV_1 compared to placebo.

Figure 2. Study 1, Mean Change from Baseline of Pre-dose FEV_1 (mL)



Mean baseline values: 1264 ml for Advair 500/50, 1174 ml for FP 500, 1192 ml for salmeterol and 1252 ml for placebo. *p<0.001 vs placebo; ‡ p 0.038 vs placebo, salmeterol and FP

Figure 3. Study 2, Mean Change from Baseline of Pre-dose FEV_1 (mL)



Mean baseline values were 1207 ml for Advair 250/50, 1236 ml for FP 250; 1205 ml for salmeterol and 1232 ml for placebo. *p<0.05 vs placebo; ‡ p<0.05 vs placebo and salmeterol

Table 7. Mean Change From Baseline Pre-dose and 2-Hour Post-Dose FEV_1 at Endpoint-ITT

Study 1	**Salmeterol 50 mcg**	**Placebo**
Baseline mean FEV_1 (mL)	1192	1282
Mean change from baseline for pre-dose FEV_1 (mL)	107*	-4
Mean change from baseline for 2-hour post-dose FEV_1 (mL)	233*	28
Study 2	**Salmeterol 50 mcg**	**Placebo**
Baseline mean FEV_1 (mL)	1205	1232
Mean change from baseline for pre-dose FEV_1 (mL)	91*	1
Mean change from baseline for 2 hour post-dose FEV_1 (mL)	200*	58
ITT=Intent-to-treat defined as patients who had taken at least one dose of study medication. * $P<0.05$ vs. placebo		

Measure of Dyspnea using Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

The BDI/TDI was used to assess the effect of treatment on relief of dyspnea. In both studies, the mean TDI scores at endpoint were greater after treatment with salmeterol compared with placebo, but the treatment difference was significant only in Study 2 ($P = 0.043$). When the data were integrated at endpoint, salmeterol treatment showed a statistical, but not clinical, improvement ($P = 0.013$) in mean TDI score (1.3) compared with placebo (0.6).

Chronic Bronchitis Symptoms Questionnaire–Global Assessment Score (CBSQ-GAS) and Minimal Clinically Important Change (MCIC) in CBSQ-GAS

This questionnaire was used to measure changes in cough, chest discomfort and sputum production using a scale of 0-4. In both individual studies and the integrated data at endpoint, the CBSQ-GAS was numerically higher after treatment with salmeterol compared with placebo, although not statistically different. In both individual studies, the MCIC at endpoint (determined to be 1.4) was slightly higher for salmeterol than placebo. When the data were integrated, a significantly greater percentage of patients treated with salmeterol (53%) compared with placebo (45%) improved by at least the MCIC at endpoint ($P = 0.018$).

Chronic Respiratory Disease Questionnaire (CRDQ)

This questionnaire evaluated the impact of chronic respiratory disease and its treatment on quality of life across four domains: dyspnea, fatigue, emotional function and mastery over the disease. Results from both the individual and integrated data showed similar mean overall CRDQ scores for both groups.

COPD Exacerbations (Time to First Exacerbation, Study Withdrawal and Incidence)

All analyses of COPD exacerbations were conducted on the integrated dataset. The incidence of exacerbations (any severity or moderate/severe) in the salmeterol group was similar to the incidence in the

placebo group. The time to first exacerbation in the salmeterol group was significantly greater than the placebo group for first exacerbation of 'any' severity (P=0.006). However, salmeterol and placebo had a similar time to 'moderate or severe' exacerbations. Patients in the salmeterol group had a significantly greater time to study withdrawal for any reason (P = 0.016) and withdrawal for a COPD-related condition (P = 0.016). There was a similar time to withdrawal for COPD exacerbation (P = 0.050) compared to placebo patients.

Morning PEF

In Studies 1 and 2, the salmeterol group demonstrated a significantly greater mean change in overall morning PEF (16.8 and 14.7 L/min, respectively) compared with the placebo group (-2.7 L/min and 0.8/min, respectively; P<0.001). The integrated analysis showed a greater change in the salmeterol group compared with the placebo group (P<0.001).

Daily albuterol use

In Studies 1 and 2, the salmeterol group used significantly less overall albuterol (mean changes from baseline were –0.9 and –0.7 puffs per day, respectively; P≤0.044) compared with the placebo group (+0.5 and +0.1 puffs per day, respectively). In the integrated analysis, the salmeterol group used less overall albuterol than the placebo group (P<0.001).

Nighttime awakenings requiring albuterol use

Results from Studies 1 and 2 showed that the salmeterol group had fewer nighttime awakenings requiring albuterol use, but the difference was only significant for Study 1 (P<0.001). The integrated data showed a significant difference in nighttime awakenings requiring albuterol use for salmeterol compared to placebo (P<0.001).

Safety

The safety profile for patients with COPD treated with salmeterol was comparable to that for patients treated with placebo. Overall, clinically significant cardiovascular abnormalities occurred in 1% of patients in the salmeterol group compared to 3% of patients in the placebo group.

In addition, bronchodilator-related responses to treatment with salmeterol favored patients with more reversible airways (response post-albuterol of ≥200 mL and ≥12% improvement in FEV_1 over baseline). However, salmeterol proved efficacious in patients who were either reversible or non-reversible to albuterol. Median treatment compliance (recording total doses from dose counters) was over 95% for the salmeterol and placebo groups.

52-Week Trial Using Serevent Diskus for COPD

In a randomized, double-blind, placebo-controlled study, the safety and efficacy of *Serevent Diskus* 50 mcg twice daily was evaluated in 733 patients with COPD in a 52-week study. [49] The study included treatment arms for *Advair Diskus* and fluticasone propionate, but only the arms including *Serevent* compared to placebo are reported here. Inclusion and exclusion criteria were consistent with the 24 week studies described above except that all patients were required to have an increase of less than 10% of predicted in FEV_1 after albuterol, were required to have at least one COPD exacerbation per year in the previous 3 years and at least one exacerbation in the previous year.

The primary efficacy measure was the mean change from baseline in pre-dose FEV_1. Secondary efficacy measures were the number of moderate or severe COPD exacerbations and quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ). Other efficacy measures included morning PEF, breathlessness (0-4 scale), cough (0-3 scale), use of rescue albuterol, and number of nighttime awakenings.

Baseline demographics and lung function were similar across the treatment groups. The mean age was 63 years, 73% of the patients were male, 49% of the patients were current smokers, the mean number of pack-years was 43, the mean FEV_1 was 44% of predicted, and the mean FEV_1/FVC ratio was 0.51.

The mean change in pre-dose FEV_1 from baseline to endpoint was significantly increased in the *Serevent* group (16 mL) compared to the placebo group (-33 mL, P<0.001). The improvement was evident at week 2 and was sustained throughout the treatment period.

Approximately 50% of patients experienced at least one moderate or severe COPD exacerbation during the study. The average number of exacerbations per year was significantly reduced in the group receiving *Serevent* (1.04) compared to the placebo group (1.30, $P = 0.003$). The mean change in SGRQ total score was -2.0 units in the *Serevent* group and -1.9 units in the placebo group (MCIC = 4 units).

The mean morning PEF increased by 16.2 L/min in the *Serevent* group compared with 1.2 L/min the placebo group ($P < 0.001$). The mean breathlessness score was 1.59 in the *Serevent* group compared with 1.66 in the placebo group (NS). The mean cough score was 1.36 in the *Serevent* group compared with 1.44 in the placebo group (NS). The mean number of puffs of albuterol used was 2.5 puffs per day in the *Serevent* group and 2.9 in the placebo group. The mean number of nighttime awakenings was 0.5 in the *Serevent* group and 0.4 in the placebo group.

5.3 Pivotal Safety and Efficacy Trials in EIB

Adults and Adolescents

Howland et al. [8] conducted a randomized, double-blind, double-dummy, single-dose, crossover study to compare the safety and efficacy of *Serevent Diskus* 50 mcg and 100 mcg, salmeterol 50 mcg via metered dose inhaler (MDI), and placebo in 24 adolescent and adult patients (12-40 years) with exercise-induced bronchospasm (EIB). All patients had a baseline forced expiratory volume in 1 second (FEV_1) of ≥70% of predicted and a ≥20% decrease in FEV_1 following a standardized, stepped exercise challenge. All salmeterol groups were significantly better than placebo in the prevention of EIB as assessed by exercise challenge testing at 0.5 and 8.5 hours after dosing ($P<0.001$). *Serevent Diskus* 50 and 100 mcg were both effective in the prevention of EIB; in addition, there was no significant difference between doses. *Serevent* 50 mcg via *Diskus* and via MDI both provided significant protection against EIB, although salmeterol via MDI provided better protection at some time points. No serious adverse events or withdrawals due to adverse events were observed during the study.

The data from the Howland et al study [8] and a second randomized, single-dose, crossover study in adults and adolescents and adults with EIB are summarized in Table 8 below. *Serevent Diskus* 50 mcg prevented EIB when dosed 30 minutes prior to exercise. For many patients this protective effect was still apparent up to 8.5 hours post dosing.

Table 8. Two Trials with *Serevent Diskus* in Patients ≥ 12 Years Old with EIB[4]

	% Fall in FEV_1	**Placebo (n=52)**	***Serevent Diskus* (n=52)**
0.5 hr postdose exercise challenge	<10%	15 (29%)	31 (60%)
	≥10% to <20%	3 (6%)	11 (21%)
	≥20%	34 (65%)	10 (19%)
Mean maximal % fall in FEV_1 (SE)		-25% (1.8)	-11% (1.9)
	% Fall in FEV_1	**Placebo (n=52)**	***Serevent Diskus* (n=52)**
8.5 hr postdose exercise challenge	<10%	12 (23%)	26 (50%)
	≥10% to <20%	7 (13%)	12 (23%)
	≥20%	33 (63%)	14 (27%)
Mean maximal % fall in FEV_1 (SE)		-27% (1.5)	-16% (2.0)

Pediatrics

Two U.S. randomized, double-blind, double-dummy, single-dose, crossover studies were conducted to assess the efficacy of salmeterol powder in prevention of EIB in 50 children aged 4-11 years. [10] [9] Study 1 was a four-way crossover comparison of salmeterol 25 mcg and 50 mcg given via *Diskus*, albuterol 180 mcg given via MDI, and placebo. Study 2 involved a three-way crossover comparison of salmeterol 50 mcg and placebo via *Diskus* and *Diskhaler*. In both trials, the primary measure of efficacy was the percent fall in FEV_1 following exercise.

The results of these two trials indicated that single doses of salmeterol administered via the *Diskus* or *Diskhaler* prevented EIB in pediatric patients with asthma up to 12 hours after dosing. In Study 1, salmeterol 25 mcg and 50 mcg were generally equivalent to each other and superior to albuterol 180 mcg via MDI. While the lowest effective dose administered via *Diskus* in children <12 years is 25 mcg, salmeterol 50 mcg appeared to produce a more consistent response. In Study 2, salmeterol 50 mcg (via *Diskus*) was clinically equivalent with salmeterol 50 mcg via *Diskhaler*.

6. ADDITIONAL SAFETY INFORMATION

6.1 Serious Asthma-Related Outcomes

SMART Study

The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta$_2$-agonist–naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol inhalation aerosol 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy. (12) (50)

The primary endpoint of this study was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events. In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). (50) In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (Table 9).

Table 9. Asthma-Related Deaths in the 28-Week Salmeterol Multicenter Asthma Research Trial (50)

	Salmeterol N (%*)	**Placebo N (%*)**	**Relative Risk† (95% CI)**	**Excess Deaths Expressed per 10,000 Patients‡ (95% CI)**
Total Population§ Salmeterol: N = 13,176 Placebo: N=13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)

	Salmeterol N (%*)	Placebo N (%*)	Relative Risk† (95% CI)	Excess Deaths Expressed per 10,000 Patients‡ (95% CI)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

*Life table 28 week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

†Relative risk is the ratio of the rate of asthma related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma related death occurred in the salmeterol group than in the placebo group in a 28 week treatment period.

‡Estimate of the number of additional asthma related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28 week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

§The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those subjects whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

SMART Study - Pediatric Data

Results in Pediatric Patients 12 to 18 Years of Age

A subgroup analysis of pediatric patients 12 to 18 years of age enrolled in the SMART study was conducted. A total of 1,653 pediatric patients were randomized to receive salmeterol 42 mcg twice daily, and 1,622 were randomized to the placebo group.(51) Baseline characteristics were similar between treatment groups. The majority of patients were male (51%-53%) with a mean age of 14.7-14.8 years and a mean FEV_1 of 89.1%-89.5% predicted. The treatment groups also were balanced with regard to ethnic origin. Pre-study asthma characteristics were similar across both treatments. The cohorts had a history of frequent emergency department (ED) visits for asthma (approximately 25% in the previous 12 months) and 6% of subjects in both groups had been hospitalized for asthma in the previous year. Nocturnal asthma symptoms affecting sleep occurred in approximately 50% of subjects.

Of the 3,275 subjects enrolled in the 12 to 18 year-old age group, 51 (2%) were hospitalized during the 28-week treatment period (). In this age group, 2 subjects in each treatment group experienced a primary outcome event; 1 of these events was a fatality (salmeterol group). Secondary outcome events were similar and the incidence did not exceed 2 events for either treatment, with the exception of all-cause hospitalization, experienced by significantly more subjects in the salmeterol group compared with the placebo group. The overall incidence of primary and secondary endpoints was similar between the patients 12 to 18 years of age and the adult patients.

Table 10. Overall Incidence of Primary and Secondary Endpoints in Pediatric Patients 12-18 Years of Age

Endpoint	12-18 Year-Olds (N=3,275)		≥19 Year-Olds (N=23,070)	
	Salmeterol 50 mcg BID	Placebo	Salmeterol 50 mcg BID	Placebo
n (%)	1,653 (50)	1,622 (50)	11,515 (50)	11,555 (50)
Primary Endpoint, n (%)				
Combined respiratory-related death or life-threatening experience	2 (<1)	2 (<1)	48 (<1)	34 (<1)
Secondary Endpoints, n (%)				
Respiratory-related death	1 (<1)	0	23 (<1)	11 (<1)
Combined asthma -related death or life-threatening experience*	2 (<1)	2 (<1)	35 (<1)	20 (<1)
Asthma-related death	1 (<1)	0	12 (<1)	3 (<1)
Combined all-cause death or life-threatening experience*	2 (<1)	2 (<1)	68 (<1)	57 (<1)
All-cause death	1 (<1)	0	41 (<1)	32 (<1)
All-cause hospitalization	35 (2)	16 (<1)	434 (4)	404 (3)
*Life threatening experience was defined as an event requiring intubation or mechanical ventilation.				

In addition, a post-hoc review of FDA MedWatch forms was performed to evaluate the relative risk of respiratory-related (including asthma) and asthma-related hospitalizations by treatment in the 12 to 18 year-old age group over the entire treatment period (). Of the 1,653 salmeterol-treated subjects in this age group, 18 (1%) were hospitalized due to a respiratory-related serious adverse events, 13 (<1%) of which were asthma-related. Of the 1,622 subjects in the placebo group, 9 (<1%) were hospitalized due to a respiratory-related serious adverse events, all of which were asthma-related. The comparison of asthma-related hospitalizations was not statistically significant between treatments. Regardless of reported ICS use at baseline, there was a higher number of respiratory-related hospitalizations with salmeterol compared with placebo (ICS use at baseline - salmeterol 10 vs. placebo 6; no ICS use at baseline - salmeterol 8 vs. placebo 3). There was no trend in any particular type of event within or across treatment groups for subjects 12 to 18 years of age who were hospitalized due to a non-respiratory-related event.

Table 11. Cumulative Relative Risk of Respiratory-Related Hospitalizations in Pediatric Patients 12-18 Years of Age

	Salmeterol 50 mcg BID	Placebo	Relative Risk (95% CI)
Subjects with All-Cause Hospitalization*	35 (2)	16 (<1)	2.0668 (1.1489, 3.7181)
Subjects with a Respiratory-Related Hospitalization (including asthma)	18 (1)	9 (<1)	1.8974 (0.8551, 4.2102)
Subjects with an Asthma-Related Hospitalization	13 (<1)	9 (<1)	1.3689 (0.5869, 3.1930)
Subjects with Other Respiratory-Related Hospitalization†	5 (<1)	0	N/A
Subjects with Non-Respiratory-Related Hospitalization	17 (1)	7 (<1)	2.2908 (0.9528, 5.5078)

CI = confidence interval

*All-cause hospitalizations included respiratory-related hospitalizations and non-respiratory-related hospitalizations which includes, but is not limited to, depression, appendicitis, miscarriage, dehydration, broken leg, auto accident, overdose of aspirin, and hydrocephaly.

†Other respiratory-related events include pneumonia, viral infection of the lung, and acute pharyngitis.

Serevent National Surveillence Study

The *Serevent* Nationwide Surveillance (SNS) study was a 16-week study in over 25,000 patients with asthma comparing salmeterol to regular use of salbutamol (albuterol).[52] Patients were randomized 2:1 to receive salmeterol 50 mcg twice daily or albuterol 200 mcg four times daily. The results of SNS noted a higher, though non-significant, number of asthma-related deaths (12 vs. 2; *P*=0.105) in salmeterol recipients compared with regular use of albuterol (Table 12).

Table 12. Results of the SNS Study[52]

Outcome	Salmeterol (n=16,787)	Albuterol (n=8393)	Relative Risk *P*-Value
All Serious Events and Withdrawals	4272 (25.5%)	2209 (26.3%)	0.97 (*P* =0.200)
Asthma-related Deaths	12 (0.07%)	2 (0.02%)	3.0 (*P* =0.105)
Asthma-related Hospitalizations	193 (1.15%)	102 (1.22%)	0.95 (*P* =0.651)
Asthma-related Withdrawals	488 (2.91%)	318 (3.79%)	0.77 (*P* =0.0002)

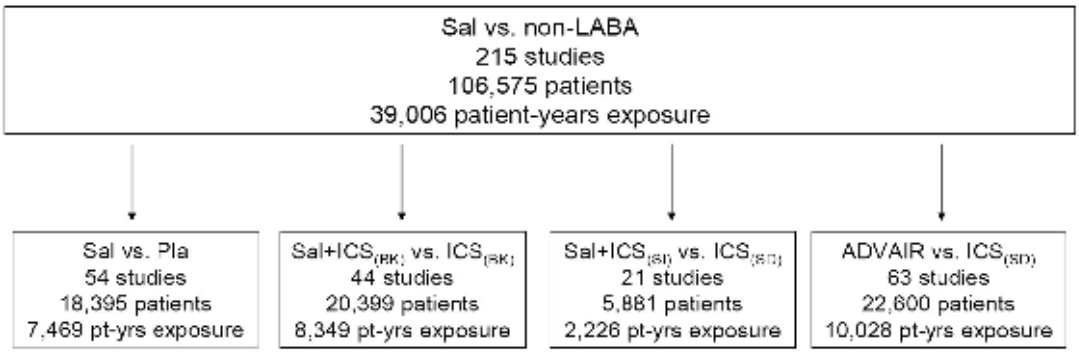
GSK Meta Analysis of Serious Asthma-Related Outcomes - Adults and Adolescents

A meta-analysis of all randomized, double-blind, chronic dosing studies of salmeterol-containing products conducted by GlaxoSmithKline (GSK) evaluated the safety profile of salmeterol when used with an ICS both in a single inhaler and in separate inhalers, or when used without an ICS.[53] A total of 215 studies including 106,575 patients were included in the analysis. These totals include data from both Serevent Nationwide Surveillance Study (SNS) and SMART. The outcomes of interest were asthma-related death, asthma-related hospitalization, asthma-related intubation, and all-cause death.

Analysis populations were constructed for each of the five treatment comparisons of interest. For a study to be included in a specific analysis population, both treatment categories for comparison must have been present within the same study (Figure 4). This approach allows for control of important study differences such as different doses of ICS, changing standards of care, and different disease severity which could confound results. The salmeterol versus non-long-acting beta-agonist comparison (designated as Sal vs non-LABA; 215 studies, N=106,575) includes the largest number of studies and patients, but represents the most heterogeneous comparison since it includes salmeterol in any form (i.e., salmeterol alone or salmeterol plus ICS or *Advair*) compared with any non-LABA matched treatment study arm (i.e., ICS, leukotriene modifier, placebo, scheduled short-acting $beta_2$-agonist, etc.). The salmeterol versus placebo comparison (designated as Sal vs Pla; 54 studies, N=18,395) evaluates the safety of salmeterol in the absence of an ICS. In evaluating the use of salmeterol with an ICS, the ICS could be administered three

different ways: 1) the addition of salmeterol to background ICS (ICS_{BK}) which refers to patients who reported taking ICS prior to the study and were instructed to continue that ICS throughout the treatment period of the study (designated as Sal + ICS_{BK} vs ICS_{BK}; 44 studies, N=20,399); background ICS was not dispensed as part of the protocol nor was there systematic reinforcement or any measure of continued adherence to the medication 2) the addition of salmeterol to ICS administered as blinded study medication (ICS_{SD}) that was part of the study protocol administered in separate inhaler (SI) devices (designated as Sal + ICS_{SI} vs ICS_{SD}; 21 studies, N=5,881) 3) and salmeterol and ICS (fluticasone propionate) in a single device as *Advair* (designated as *Advair* vs ICS_{SD}; 63 studies, N=22,600). Only the *Advair* vs ICS_{SD} analysis population assures the concurrent use of ICS each time a patient was exposed to salmeterol. Therefore, this population was the primary population to inform on the safety profile of salmeterol in the presence of an ICS.

Figure 4. Diagram of Analysis Populations for Meta-Analysis



BK=background; SD=study drug; SI=separate inhalers

All serious adverse events were adjudicated from blinded case narratives by independent, external physicians. The primary measure for the analysis of the primary outcomes is the risk difference of rates between the treatment comparisons of interest.

A total of 35 asthma-related deaths were reported in the total population comparison of salmeterol versus non-LABA.[53] Of the 35 asthma-related deaths reported, 30 occurred in SMART and SNS together, accounting for 86% of the asthma-related deaths. Of the five asthma-related deaths not from SNS and SMART, three occurred in patients receiving salmeterol (two receiving salmeterol alone and one receiving salmeterol plus FP in separate inhalers) and two occurred in patients receiving other treatment (one receiving albuterol four times daily and one receiving placebo). There were no asthma-related deaths in the 11,437 patients who received *Advair*.

For studies where the concurrent use of salmeterol and ICS can be reasonably assured (e.g., *Advair* and Sal + ICS_{SI}), there was no evidence of increased risk for asthma-related death. However, when salmeterol was used in the absence of an ICS, an increase in asthma-related death were observed (Figure 5).

A total of 1,103 of the 106,575 patients in the analysis reported an asthma-related hospitalization (Figure 6). Overall, there was a statistically significant increase in the risk difference for asthma-related hospitalization for salmeterol compared with non-LABA and for Sal + ICS_{BK} compared with ICS_{BK}. The risk difference for asthma-related hospitalization was higher in patients who used salmeterol without an ICS and when ICS use was not controlled or dispensed by the protocol (i.e., salmeterol as blinded study drug added to background ICS). Risk difference decreased when patients used both salmeterol and ICS as dispensed study drugs. No increased risk was observed in patients who received *Advair* compared with an ICS.

Results for asthma-related intubations and all-cause death were consistent with the results for asthma-related death and hospitalizations (data not shown).

Figure 5. Meta-Analysis: Risk Difference for Asthma-Related Death (0.5 Continuity Correction)

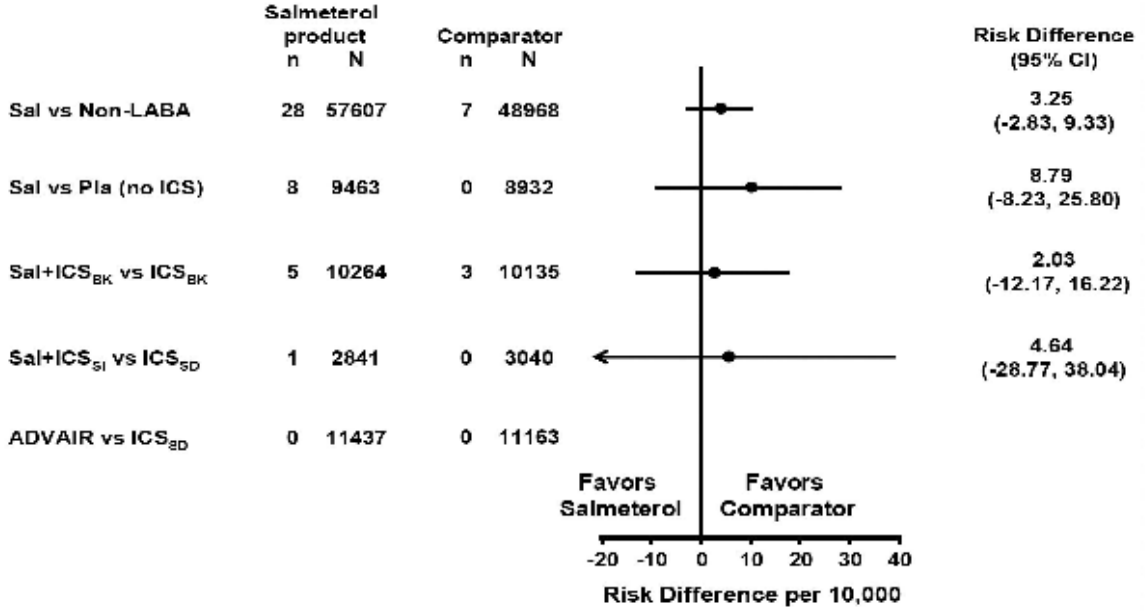
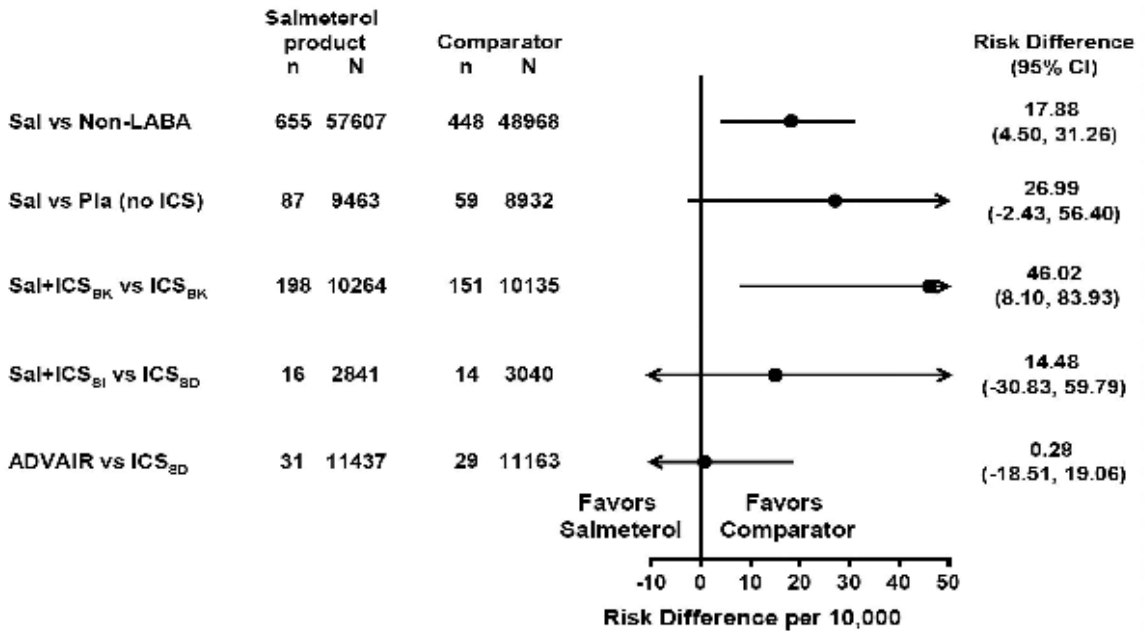


Figure 6. Meta-Analysis: Risk Difference for Asthma-Related Hospitalizations (0.5 Continuity Correction)

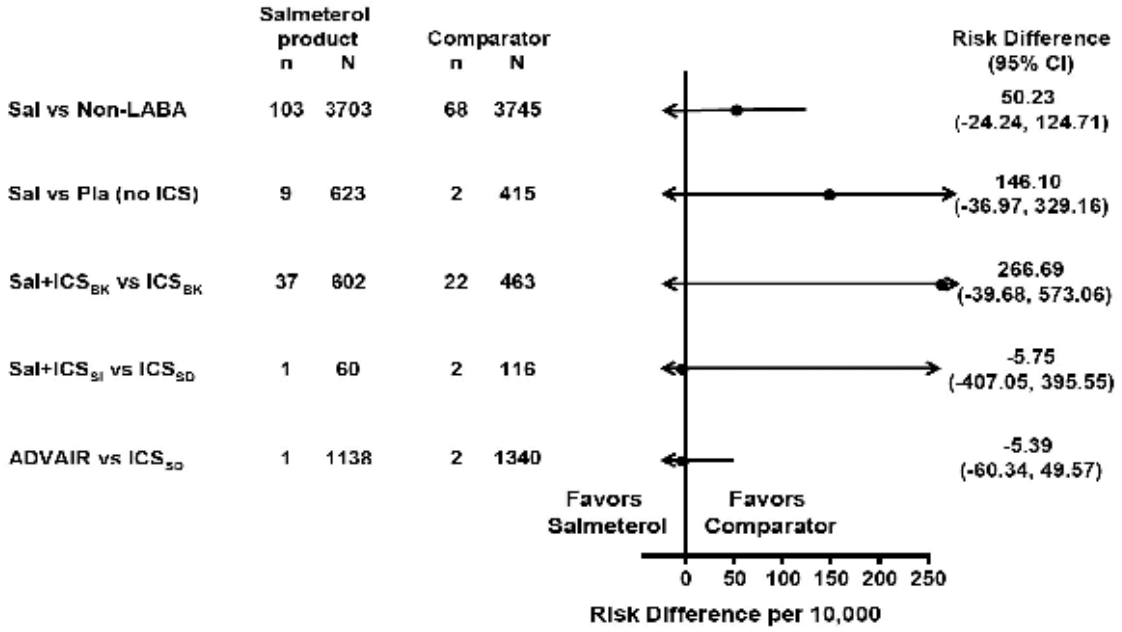


GSK Meta Analysis of Serious Asthma-Related Outcomes - Pediatrics

As part of this meta-analysis, an analysis of 37 studies which included pediatric patients less than 12 years of age was conducted.(53) Only one pediatric asthma-related death was reported in a patient was receiving albuterol four times daily. There was one intubation each for a patient receiving albuterol four times daily and in one receiving salmeterol without concurrent ICS.

Overall, the risk of asthma-related hospitalizations from studies in children were consistent with the total population and suggest patients taking salmeterol in the absence of ICS may be at increased risk of asthma-related hospitalizations (Figure 7). However, when salmeterol and ICS were used concurrently either as study drug (Sal + ICS_{SI}) or as *Advair*, there appeared to be no increased risk of asthma-related hospitalizations in children. Also, similar to the data in the overall population, the risk was elevated when salmeterol was administered with background ICS therapy (ICS_{BK}) compared with background therapy alone.

Figure 7. Meta-Analysis: Risk Difference for Asthma-Related Hospitalizations (0.5 Continuity Correction): Pediatric Population



6.2 Studies Assessing Cardiovascular Safety in Patients with Asthma

Multidose Studies

Safety data were analyzed from two, identically designed, randomized, double-blind, placebo controlled studies enrolling 556 patients with asthma. (54) Patients were randomized to salmeterol inhalation aerosol 42 mcg twice daily (n=184), albuterol 180 mcg four times daily (n=185), or placebo (n=187) for 12 weeks. In addition, patients could use supplemental albuterol for acute asthma symptoms as needed. Patients had a 12-lead ECG at study weeks 4, 8, and 12 and a subset of 240 patients underwent continuous 24-hour Holter monitoring at baseline and various points throughout the study.

There were no clinically significant changes in pulse or blood pressure measurements within the treatment groups over the 12 weeks of treatment. (54) In addition, there was no clinically significant changes in standard 12-lead ECG results in any treatment group. At baseline, 4% of the placebo and salmeterol patients had QTc intervals >440 msec (maximum normal limit) as compared to 1% and 6%, respectively, following 12 weeks of treatment. The results of the Holtor monitoring found that the ventricular and supraventricular ectopy frequency was low, and similar across the three treatment groups. Cardiovascular adverse events in the salmeterol arm, stratified by daily supplemental albuterol use is shown in Table 13 below.

Table 13. Cardiovascular Adverse Events in Patients Treated with Salmeterol Stratified by Daily Albuterol Use [54]

Adverse Events	Mean Supplemental Albuterol Use		
	<1 puff/day n=105	1-4 puffs/day n=60	>4 puffs/day n=17
Palpitations	4%	0	0
Tachycardia	1%	3%	6%
Precordial pain	0	2%	0
Pallor/flushing	0	2%	0
Any cardiovascular event	4%	5%	6%

In a 12-month study evaluating the long-term safety of salmeterol 50 mcg twice daily (n=334), palpitations occurred in 3.9% of patients and tachycardia in 0.6%. [55] No other significant cardiovascular changes were noted.

Another placebo-controlled 12-month study in 352 patients with mild persistent asthma revealed no clinically significant cardiovascular changes or arrhythmias with regular use of salmeterol powder 50 mcg given twice daily for one year. [56] Serial pulse rate measurements performed over 12 hours demonstrated no significant between-group differences in mean pulse rate on treatment day 1 and at treatment week 48. Postdose increases in systolic blood pressure (BP) on day 1 and at weeks 8, 20, and 48 were slightly higher (1-2 mm Hg) for the salmeterol group compared to placebo ($P \leq 0.031$), although these modest increases in systolic BP were not considered to be clinically significant. Changes in diastolic BP were similar (± 2 mm Hg) for both treatment groups, and no statistically significant between-group differences were observed. During treatment, mean predose and postdose QTc intervals were comparable for both groups at all evaluation time points. Following salmeterol administration on treatment day 1 and at weeks 8, 20, and 48, significant changes from predose ECGs were observed in 2%, 1%, 1%, and <1% patients, respectively. Overall, ≤ 1% of patients treated with salmeterol powder exhibited abnormal ECGs that were considered clinically significant. No clinically significant between-group differences were observed in median number of ventricular or supraventricular ectopic events, incidence of ventricular ectopic couplets and runs, or incidence of >100 ventricular or supraventricular ectopic events in 24 hours.

Metaanalysis

A metaanalysis of 19 clinical studies performed between 1985-1999 was conducted in which patients received salmeterol 100 mcg either as a single-dose or twice daily. [57] Seven studies also included a salmeterol 50 mcg twice daily treatment arm for comparison. This safety analysis included 10 single-dose studies enrolling 141 patients and nine multi-dose studies enrolling 1,504 patients which were 2 weeks to 12 months in duration. Three single-dose studies enrolled healthy volunteers, one multi-dose study enrolled patients with COPD and the remaining studies were conducted in patients with asthma. Cardiovascular adverse events are listed in Table 14 and Table 15.

Table 14. Cardiovascular Adverse Events in Salmeterol Multi-Dose Studies [57]

Parameter	N	No. Events	Change	Incidence
Salmeterol 100 mcg Twice Daily				
Mean change in heart rate (bpm)	755	-	1.8	-
Mean change in systolic blood pressure (mm Hg)	745	-	-0.2	-
Tremor	1504	-	-	5.6%
Palpitations	1504	-	-	1.7%
Decrease in serum potassium*	1504	13	-	0.9%
Increase in serum glucose†	1504	5	-	0.3%
ECG event‡	1504	9	-	0.6%
Salmeterol 50 mcg Twice daily				
Mean change in heart rate (bpm)	760	-	1.2	-

* 12 unspecified decrease; 1 decrease of 0.17 mmol/L; 36 cases of increase

† 5 unspecified glucose events

‡ One study event and 8 post-treatment events; 12 pre-treatment arrhythmias

Parameter	N	No. Events	Change	Incidence
Mean change in systolic blood pressure (mm Hg)	760	-	-0.35	-
Tremor	890	-	-	1.7%
Palpitations	890	-	-	0.9%

* 12 unspecified decrease; 1 decrease of 0.17 mmol/L; 36 cases of increase

† 5 unspecified glucose events

‡ One study event and 8 post-treatment events; 12 pre-treatment arrhythmias

Table 15. Cardiovascular Adverse Events in Salmeterol 100 mcg Single-Dose Studies [57]

Parameter	N	No. Events	Change	Incidence
Mean change in heart rate (bpm)	84	-	2.3	-
Maximum change in heart rate (bpm)	46	-	10.4	
Mean change in systolic blood pressure (mm Hg)	60	-	0.4	-
Maximum change in systolic blood pressure	46	-	13.9	-
Tremor	141	-	-	5.7%
Palpitations	141	-	-	2.8%
Decrease in serum potassium*‡	141	3	-	2.1%
Increase in serum glucose†‡	141	1	-	0.7%
ECG event§	141	24	-	17%

* Two unspecified decrease; 1 decrease of 0.2 mmol/L; 1 trend toward increase

† One increase of 0.2 mmol/L

‡ One study of 24 patients reported a trend for decreasing potassium and increasing glucose

§ First degree AV block (1 each for salmeterol and placebo); isolated supraventricular premature beats (14 salmeterol and 18 placebo); isolated ventricular premature beats (8 salmeterol and 9 placebo); paired ventricular premature beats (1 salmeterol).

Cumulative Dose Studies

A double-blind, placebo-controlled study in 10 healthy adult male volunteers was conducted to evaluate the pharmacological activity of high doses of salmeterol, and to compare these effects with those of high-dose albuterol. [58] Salmeterol inhalation aerosol was given in increasing doses of 100 mcg, 200 mcg, and 400 mcg. The sequence of administration of albuterol 400 mcg and placebo was randomized. Laboratory safety tests were performed before and after each treatment. Pulse rate, arterial blood pressure, and 12-lead ECG were measured before and up to 8 hours after each treatment.

No dose-related effects were observed for arterial blood pressure. Significant (P<0.05) dose-related increases in mean, peak, and duration of response were observed in pulse rate after salmeterol compared with placebo. The mean increase in pulse rate compared with placebo was 6, 7, and 16 beats per minute for salmeterol 100 mcg, 200 mcg, and 400 mcg, respectively. Compared with albuterol 400 mcg, salmeterol 200 mcg and 400 mcg produced significantly greater mean pulse rate. Minor transient ECG changes related to the pharmacological activity of ß$_2$-adrenoceptor agonists (i.e., minor non-specific T-wave changes, prolongation of QTc interval up to 63 msec) were observed after both salmeterol 400 mcg and albuterol 400 mcg. Overall, responses observed with salmeterol 100 mcg were similar to those observed with albuterol 400 mcg. Salmeterol was well-tolerated at doses up to 400 mcg, and most adverse events were attributable to the known pharmacology of the compounds.

Single Dose Studies

A double-blind, single-dose, dose-ranging, placebo-controlled, six-way crossover study of 24 patients with mild-to-moderate asthma included 24-hour Holter monitoring to assess the cardiovascular effects of various doses of salmeterol. [59] Holter monitoring began before patients received either placebo, albuterol 200 mcg, or salmeterol 12.5 mcg, 25 mcg, 50 mcg, or 100 mcg via inhalation aerosol and continued for 24 hours while patients remained in the clinical study unit. Pulse and blood pressure were measured 0.5 hours predose, immediately predose (0 hours), and at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, and 24 hours after drug administration.

Holter monitoring showed no statistically significant differences between treatment groups for high frequencies of supraventricular premature beats (SVPB) (i.e., greater than 30 SVPB per hour or greater than 100 SVPB per 24 hours) or ventricular premature beats. Mean maximum heart rates did not differ significantly after treatment with albuterol, salmeterol 12.5 mcg, and salmeterol 25 mcg compared with placebo. However, mean maximum heart rate was 2 to 5 beats per minute higher after salmeterol 50 mcg and 100 mcg compared with placebo (P <0.05). Palpitations were reported after administration of the two highest salmeterol doses (by one patient after salmeterol 50 mcg and by four patients after salmeterol 100 mcg). Palpitations were not reported after either albuterol or placebo administration. No clinically significant abnormalities were observed on the single time point determinations of 12-lead ECG for any of the 24 patients during any of the six treatment periods.

6.3 Studies Assessing Safety in Patients with COPD

3 Year Study - TORCH

The TORCH (TOwards a Revolution in COPD Health) study was a 3-year, randomized, double-blind, parallel-group, placebo-controlled, multicenter study which compared the safety and efficacy of salmeterol, fluticasone propionate, salmeterol plus fluticasone propionate, and placebo in 6112 patients with moderate-to-severe COPD. [60] Study medication was given twice daily. The primary study endpoint was the time to death from any cause by 3 years. Other endpoints included exacerbations, hospitalizations, health status, lung function, and safety endpoints. The most common serious cardiovascular adverse events reported in the salmeterol and placebo groups are listed in the table below.

Table 16. Most Common Serious Cardiovascular Adverse Events in the 3-Year TORCH Study (Reported in at Least 1% of Patients in Either Treatment Group) [61]

Number (%) of Patients Reporting Events [Rate per 1000 treatment years*]	Placebo (n=1544)	Serevent (n=1542)
Myocardial Infarction	20 (1.3%) [6.7]	27 (1.8%) [7.6]
Atrial fibrillation	20 (1.3%) [6.7]	23 (1.5%) [6.5]
Cardiac failure congestive	18 (1.2%) [5.5]	18 (1.2%) [7.1]
Cardiac failure	15 (1.0%) [5.5]	18 (1.2%) [7.6]
Chest pain	8 (0.5%) [3.1]	17 (1.1%) [5.4]

*Accounts for the different lengths of treatment exposure in the groups.

Pooled Analyses of Salmeterol Clinical Trials

A pooled analysis of 7 randomized, double-blind, parallel group, multiple-dose studies was conducted that included a salmeterol 50 mcg twice daily treatment arm for COPD patients. [62] All studies monitored adverse events and at least one of the following cardiovascular endpoints: ECG, QT intervals, vital signs or 24-hour Holter monitoring. The primary comparison for all endpoints was salmeterol 50 mcg twice daily versus placebo.

A total of 2,853 COPD patients met inclusion requirements for the pooled analysis. Treatment duration ranged from 12 weeks to 1 year. Patients were between 35-90 years of age, had an extensive smoking history (mean 52 pack-years) and had moderate to severe impaired lung function (mean FEV_1 42% predicted). Approximately 40% of patients had an underlying cardiac condition at baseline. There were no clinically significant differences between salmeterol and placebo in vital signs, qualitative ECGs, QT intervals, 24-hour heart rate or ventricular ectopic beats (VEs) and supraventricular ectopic beats (SVEs). At endpoint, the 95% confidence interval for the difference between salmeterol 50 mcg twice daily and placebo for mean 24-hour heart rate was (-0.64 beats per minute [bpm], 2.95 bpm, difference=1.2 bpm) and for QTcB (QTc interval corrected by Bazett's formula) (-2.4 msec, 2.6 msec, difference=0.1msec). The incidence of cardiovascular adverse events was the same in the salmeterol and placebo groups (8%). Inferential analysis comparing the rate of adverse events demonstrated no increased risk of CV adverse events [relative risk=1.03, 95% CI: (0.8, 1.3), P = 0.838].

A subset analysis of the 7 pooled studies above was performed to assess cardiovascular safety in those patients with COPD who were ≥ 65 years of age. [62] This study evaluated 1405 patients with COPD, treated for 12 weeks to 1 year who were between 65-90 years old. The incidence of cardiovascular adverse events was comparable between the salmeterol 50 mcg twice daily and placebo groups (9%) with no clinically significant differences between groups in regards to vital signs, qualitative ECGs, QT intervals, 24-hour heart rate or ventricular ectopic or supraventricular ectopic events.

Clinical Trials Comparing Salmeterol to Placebo

Trials of patients with COPD found that clinically significant adverse cardiovascular events with salmeterol occurred at rates that were comparable to placebo (Table 17).

Table 17. Clinical Trials Comparing Salmeterol to Placebo

Study Design	Patient Demographics	Dosage	Results
Randomized, double-blind, placebo-controlled, parallel group x 16 weeks. [63] Previous cardiovascular conditions were not noted.	674 pts (age range 39-75 yrs) with COPD	-SAL 50 mcg BID -SAL 100 mcg BID -PBO All treatments administered via MDI w/ or w/o spacer. Pts receiving methylxanthines pre-trial were allowed to continue. ALB allowed for symptom control.	Overall, there were no effects on vital signs or ECG rhythm strips thought due to study medications.
Randomized, double-blind, placebo-controlled, crossover study x 15 days. [64] 43% had pre-existing cardiovascular disease.	44 pts (mean age 73 yrs) with COPD	-SAL 50 mcg BID -PBO	No significant changes found in mean 24-hour HR on day 1 or 15 compared to PBO. A small increase in maximum HR was found on day 1 for SAL group (mean 3.3 bpm) but that effect was not seen in the corresponding overnight measurements. No other differences versus PBO were found in BP, ECG intervals, rhythm disturbances, pulse oximetry, and plasma potassium or glucose.

AEs=adverse events; ALB=albuterol; BID=twice daily; BP=blood pressure; bpm=beats per minute; ECG=electrocardiogram; FOR=formoterol; HR=heart rate; LABA=long-acting beta-agonist; MDI=metered dose inhaler; PBO=placebo; pts=patients; QID=four times daily; SABA=short-acting beta-agonist; SAL=salmeterol; SR=sustained release; yrs=years

Comparative Trials

Continuous ECG (Holter) monitoring was performed on 284 patients in two large COPD clinical trials during five 24 hour periods.[4] At baseline, non sustained, asymptomatic ventricular tachycardia was recorded for 7 (7.1 %), 8 (9.4 %), and 3 (3.0 %) patients in the placebo, salmeterol MDI, and ipratropium groups, respectively. During treatment, non-sustained, asymptomatic ventricular tachycardia that

represented a clinically significant change from baseline was reported for 11 (11.6 %), 15 (18.3 %), and 20 (20.8 %) patients receiving placebo, salmeterol, and ipratropium, respectively. Four of the cases of ventricular tachycardia were reported as adverse events (1 placebo, 3 salmeterol) by one investigator based upon review of Holter data. One case of ventricular tachycardia was observed during ECG evaluation of chest pain (ipratropium) and reported as an adverse event. No cases of sustained ventricular tachycardia were observed.

Clinical trials comparing salmeterol to other agents used in the treatment of COPD, including ipratropium, formoterol and theophylline are summarized in Table 18 (below).

Table 18. Comparative Studies Evaluating Salmeterol

Study Design	Patient Demographics	Dosage	Results
Stratified, randomized, double-blind, double-dummy, placebo-controlled, parallel group x 12 weeks. (65) Cardiovascular history of pts enrolled was not noted.	361 pts with COPD (mean age range 63-64 yrs)	-SAL 42 mcg BID -Ipratropium 36 mcg QID -PBO Theophylline products were discontinued prior to initiation of study.	There were no clinically significant changes or differences with regard to vital signs or 12-lead ECG at baseline, during treatment, or study completion. As measured by 24-hour ECG monitoring, the number of events of ventricular or supraventricular ectopic beats was highly variable; however, no significant differences were noted at baseline or at completion of the study.
AEs and vital signs were collected every 2 weeks, 12-lead ECGs were recorded at weeks –2, 0, 4, 8, 12. Continuous ambulatory ECG monitoring (for 24 hours) was reported at approximately half the study sites at weeks –2, 0, 4, 8, 12.		ALB allowed for symptomatic relief.	Of note, the number of events was lower at week 4 for salmeterol and ipratropium when compared to placebo, but at week 8, the frequency of supraventricular events was higher for ipratropium than for placebo ($P = 0.015$).
Stratified, randomized, double-blind, placebo controlled x 12 weeks. (66) Patients were excluded for significant cardiovascular disease or for a significantly abnormal ECG.	405 pts with COPD (mean age range 62-64 yrs)	-SAL 42 mcg BID -Ipratropium 36 mcg QID -PBO	Over the treatment period, no clinically important differences were seen in vital signs, ECG rhythm strips or 24-hour Holter monitoring. There were no significant differences in number of ventricular and supraventricular ectopic beats picked up by Holter monitoring. There also were no symptomatic or life-threatening arrhythmias reported or observed.

Study Design	Patient Demographics	Dosage	Results
		All treatments administered via MDI. Theophylline products were discontinued prior to initiation of study. ALB allowed for symptomatic relief.	
Randomized, single-blind, balanced, crossover, placebo-controlled. (67)	12 patients with COPD (age range 51-70)	-SAL 50 mcg -FOR 12 mcg -FOR 24 mcg Oral bronchodilators discontinued 1 week prior to study; SABA discontinued 12 hrs prior; LABA discontinued 24 hrs prior. Coffee, cola, tea and smoking held prior to and during study.	Holter monitoring revealed a higher mean heart rate after FOR 24 mcg compared with SAL, FOR 12 mcg, and PBO. Both SAL and FOR 12 mcg resulted in a higher mean heart rate than placebo, but there was no difference between the two active drugs. Supraventricular and ventricular premature beats occurred more often after FOR 24 mcg than the other treatments.
All patients had pre-existing mild-to-moderate cardiac arrhythmias and hypoxemia (PaO_2<60).			In addition, FOR 24 mcg significantly reduced plasma potassium levels for 9 hours compared with placebo.
Baseline 12-lead ECG done prior to study.			In contrast, FOR 12 mcg significantly reduced potassium levels after 2 and 4 hours and SAL significantly reduced potassium levels between 4 to 9 hours.
All patients underwent Holter monitoring for 24 hours during each of the four treatment arms.			

Study Design	Patient Demographics	Dosage	Results
Plasma potassium was measured at baseline, before drug administration, at 2-hour intervals for six hours, and at 9, 12, and 24 hours following drug administration.			
Randomized, double-blind, parallel group x 12 weeks. (68) Patients with congestive heart failure were excluded. ECG and vital signs were monitored.	803 pts with COPD secondary to emphysema or chronic bronchitis (mean age range 64-65 yrs)	-SAL 42 mcg BID -SAL 42 mcg BID plus oral SR theophylline BID -Oral SR theophylline BID. Theophylline was titrated to peak serum concentrations of 10-20 mcg/mL and SAL was administered via MDI.	Drug-related cardiovascular adverse events occurred in 1-4 % of all treatment groups. There were no significant differences in blood pressure found. Clinically significant ECG changes were comparable among all treatment groups. Increases in premature ventricular contractions did not occur in the SAL group, but occurred in 3 patients each in the theophylline groups. Non-specific ST-T wave changes occurred in 2 patients in the SAL group, 4 patients in the SAL plus theophylline group and 1 patient in the theophylline alone group.
Two, randomized, double-blind, placebo-controlled, parallel registration trials x 24 weeks each to evaluate the effect of SAL on QT interval prolongation. (69) QT intervals were evaluated at baseline screening, week 12 and 24 by 12-lead ECG.	711 pts (40-90 yrs old) with COPD Mean 60 + pack-year smoking history FEV_1 of between 40-42 % predicted	-SAL 50 mcg -SAL 50 mg + FP -PBO	No increase in QT interval was noted from baseline and there were no significant differences when compared to placebo with respect to either corrected QT interval of QTcB or QTcF.
	> 40% were also noted to have previous cardiac conditions.	All treatments administered via the *Diskus* device	

Study Design	Patient Demographics	Dosage	Results
QT intervals were corrected using both the Bazett (QTcB) and Fridericias (QTcF) formula correction.			
AEs=adverse events; ALB=albuterol; BID=twice daily; bpm=beats per minute; ECG=electrocardiogram; FOR=formoterol; LABA=long-acting beta-agonist; MDI=metered-dose inhaler; PBO=placebo; pts=patients; QID=four times daily; SABA=short-acting beta-agonist; SAL=salmeterol; SR=sustained release; yrs=years;			

6.4 Studies Assessing the Lack of Masking Effects in Asthma

Salmeterol plus ICS versus Increased ICS Dose

Matz et al. [70] analyzed the asthma exacerbations occurring in two identical, multicenter, randomized, double blind, 6-month trials. Results showed that of the 925 enrolled, a total of 104 patients experienced exacerbations. The patients receiving salmeterol 42 mcg twice daily (BID) and low-dose fluticasone propionate (FP) 88 mcg BID had a significantly lower rate of exacerbations than the patients receiving a 2.5-fold higher dose of FP (220 mcg twice daily) (Table 19). All inhaled medications were administered via metered dose inhaler.

Table 19. Exacerbations Occurring in Patients with Salmeterol + FP or FP Alone

Parameter	Salmeterol + FP 88 mcg BID (n=467)	FP 220 mcg BID (n=458)	*P*-value
Patients with ≥ 1 exacerbation (%)	41 (8.8)	63 (13.8)	0.017
Total number of exacerbations	47	75	Not reported
Exacerbation rate	0.23	0.39	0.005
Mean duration of exacerbation (days)	8.4 +/- 0.9	10.5 +/-1.2	0.173

Patients in both the mild-to-moderate asthma (% predicted FEV_1 > 60-85) and severe asthma (% predicted FEV_1 = 40-60) categories, experienced fewer exacerbations while receiving salmeterol plus FP 88 mcg BID than the patients receiving FP 220 mcg BID.

Parameters including morning (AM) peak expiratory flow (PEF), asthma symptom scores, and rescue albuterol use were measured during 3 periods: 2 weeks before, during, and 2 weeks after an exacerbation. While changes in these parameters were comparable in the 2 treatment groups in the 2 weeks before and during an asthma exacerbation, significantly greater improvements in morning PEF (Figure 8), asthma symptom scores (Figure 9), and rescue albuterol use were observed in the 2 weeks after an exacerbation with the use of salmeterol plus FP 88 mcg BID compared to FP 220 mcg BID.

Figure 8. Greater Improvement in AM PEF: Salmeterol + FP After Exacerbation[70]

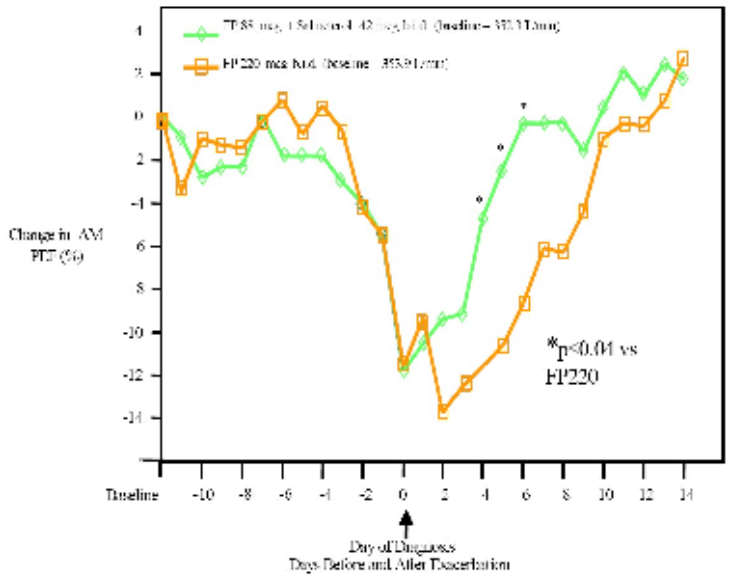
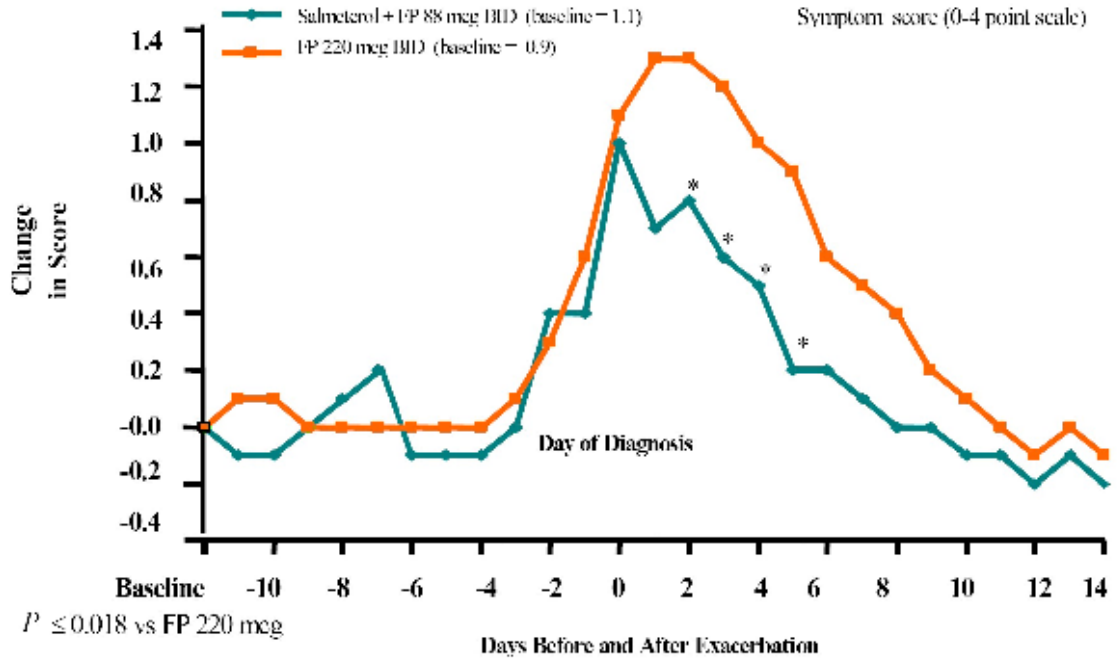


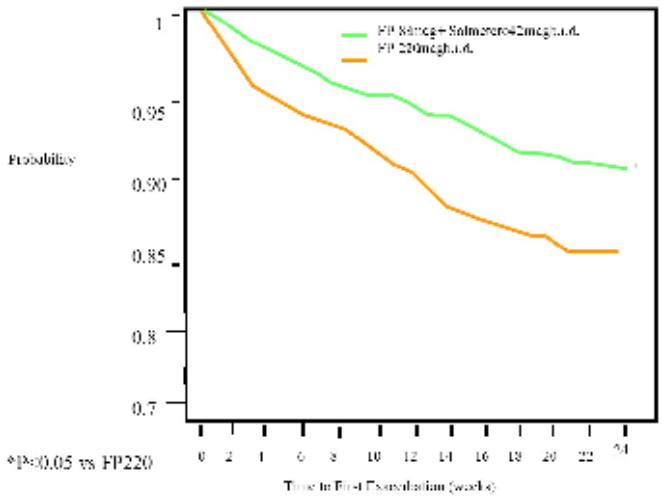
Figure 9. Change in Asthma Symptom Scores Pre- and Post-Asthma Exacerbation[70]



* $P \leq 0.018$ vs FP 220 mcg

Analysis of the time to first exacerbation revealed that the use of salmeterol plus FP was more protective than FP alone (Figure 10).

Figure 10. Kaplan-Meier Plot: Time to First Exacerbation with Salmeterol + FP compared to FP [70]



Salmeterol Plus ICS versus Placebo Plus ICS

Wilding et al. [71] conducted a double-blind, randomized, placebo-controlled, crossover study to determine the effect of adding salmeterol inhalation powder 50 mcg twice daily to current ICS treatment for six months (placebo and salmeterol were administered via Rotadisk®). A total of 101 patients with asthma (FEV_1 > 50% predicted) who were receiving at least 400 mcg daily of beclomethasone dipropionate or budesonide participated in the study. Throughout the study, patients adjusted their ICS dose according to a personalized management plan based upon PEF and asthma symptoms.

Treatment with salmeterol resulted in a 17% reduction in the mean ICS dose compared with placebo. There was no significant difference between treatment groups in the number of patients who experienced an asthma exacerbation or required treatment with oral steroids. In addition, patients treated with salmeterol had significantly improved lung function, reduced asthma symptoms and supplemental bronchodilator use, and decreased bronchial hyperresponsiveness compared with patients who received placebo.

D'Urzo et al.[72] conducted a randomized, double-blind, parallel-group study to investigate the effectiveness and safety of salmeterol in the primary-care setting. A total of 911 patients with asthma were randomized to received salmeterol inhalation aerosol 50 mcg twice daily or placebo for 24 weeks. The use of short-acting $beta_2$-agonist therapy was also permitted in both treatment groups throughout the study. All patients were required to be using optimum doses (as defined by the investigator) of anti-inflammatory therapy while still requiring inhaled short-acting $beta_2$-agonists more than twice daily. A total of 93% of patients used ICS alone, 5% of patients used oral corticosteroids plus ICS, 1% used oral corticosteroids alone, and the remainder used cromolyn or nedocromil. The primary outcome variable was the proportion of patients experiencing a serious asthma exacerbation, defined as a requirement for treatment with oral prednisone, hospitalization, or an emergency room treatment. There was no significant difference in the proportion of patients experiencing serious exacerbations between the salmeterol and placebo groups (20.8% versus 20.9%, P=0.935). Treatment with salmeterol resulted in significantly greater (P<0.01) peak expiratory flow and significantly less daily use of albuterol (P<0.001) and nighttime awakenings (P=0.028) compared with placebo.

Salmeterol Plus ICS versus Albuterol Plus ICS

Von Berg et al. [73] conducted a double-blind, randomized, placebo-controlled, parallel group study in 426 children (aged 5-15 years) with asthma to compare the efficacy of salmeterol inhalation powder 50 mcg twice daily versus as needed albuterol over 12 months. There was no significant difference between treatment groups in the number of patients who experienced an asthma exacerbation. A stratification analysis by use of concurrent ICS showed no significant difference in asthma exacerbation rates between

treatment groups. In addition, salmeterol resulted in significant and sustained improvement in lung function and a significant reduction in nighttime symptoms and supplemental nighttime albuterol use.

6.5 Studies Assessing the Occurrence of Tolerance in Adults with Asthma

Background

Although often used interchangeably, tachyphylaxis and tolerance represent two distinct pharmacologic phenomena. Tachyphylaxis is defined as the rapid appearance of a progressive decrease in response to repetitive administration of a pharmacologically or physiologically active substance. Tolerance is the ability to endure or become less responsive to stimulus, especially over a period of continued exposure. (74) Tachyphylaxis or tolerance may develop with any or all pharmacological effects of a drug. The pharmacological concerns for salmeterol would be the development of tachyphylaxis or tolerance in regard to its bronchodilatory (ability to increase the radius of the bronchi and bronchioles) or bronchoprotective (ability to protect the airways against stimuli such as methacholine, exercise, cold air, etc.) effects.

Clinical Trials: Sustained Bronchodilation

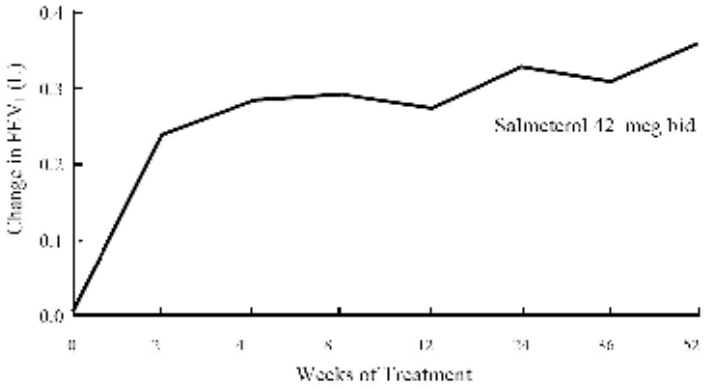
Salmeterol sustained improvements in bronchodilation for up to 12 months in adult patients regardless of concomitant inhaled corticosteroid (ICS) usage (Table 20).

Table 20. Effects of Salmeterol on Bronchodilation

Design, Patients	Treatment	Results
Britton et al. (55) 52-week, DB, R, N=667, ± ICS, FEV_1 or PEFR>50% predicted	SAL 50 mcg dry powder inhaler BID or ALB 200 mcg QID (12 wks), then BID (9 mos)	Morning, evening PEF improvement with SAL was significantly better than ALB and sustained for 52 weeks with no evidence of tolerance to bronchodilation.
Lotvall et al. (75) 52-week Open-label; N=11, on ICS mean FEV_1 68% predicted	SAL 50 mcg dry powder inhaler BID	Sustained improvement in FEV_1 with no evidence of tolerance (P<0.05 from baseline).
Lundback et al. (76) 52-week, R, DB N=388, ± ICS, FEV_1 >50% predicted	SAL 50 mcg dry powder inhaler BID or ALB 400 mcg QID (12 wks), then BID 9 mos	Sustained increase in FEV_1; mean change 0.23-0.28L with SAL and 0.1-0.15L with ALB (Figure 11). No increase in severity or frequency of asthma exacerbations in the SAL group.
Kemp et al. (77) 52-week, R, PG, PL-C; N=352, FEV_1 50-70% predicted	SAL 50 mcg dry powder inhaler BID or Placebo	Sustained improvement in mean area under FEV_1 12-hour curve; 5.06L/hours at baseline and 5.79L/hours at 48 weeks.
BID=twice daily; DB=double blind; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroids; PEF=peak expiratory flow ; PL-C=placebo-controlled, ALB=albuterol, R=randomized, QID=four times daily; mos=months; SAL=salmeterol		

Design, Patients	Treatment	Results
Rosenthal et al. [78] 24-week, R, DB, PL-C; N=408, rescue ALB, Mean FEV_1 84% predicted	SAL 42 mcg metered dose inhaler BID or Placebo	SAL improved morning PEF (26.2 L/min), morning FEV_1 (0.21-0.26 L at 6 visits), daytime asthma symptoms (20% decrease) ($P \leq 0.005$ vs. Placebo). SAL and placebo had 34 & 48 exacerbations of similar severity, respectively.
D'Alonzo et al. [79] 12-week, DB, R, PL-C N=322, ±ICS FEV_1 66% predicted	SAL 42 mcg metered dose inhaler BID or ALB 180 mcg QID or Placebo	SAL group had an increase in mean AUC for FEV_1, morning and evening PEF, and symptom-free days vs. ALB and Placebo ($P<0.001$)
BID=twice daily; DB=double blind; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroids; PEF=peak expiratory flow ; PL-C=placebo-controlled, ALB=albuterol, R=randomized, QID=four times daily; mos=months; SAL=salmeterol		

Figure 11. Maintenance of Lung Function with Long-Term Use of Salmeterol [76]



Clinical Trials: Bronchoprotection

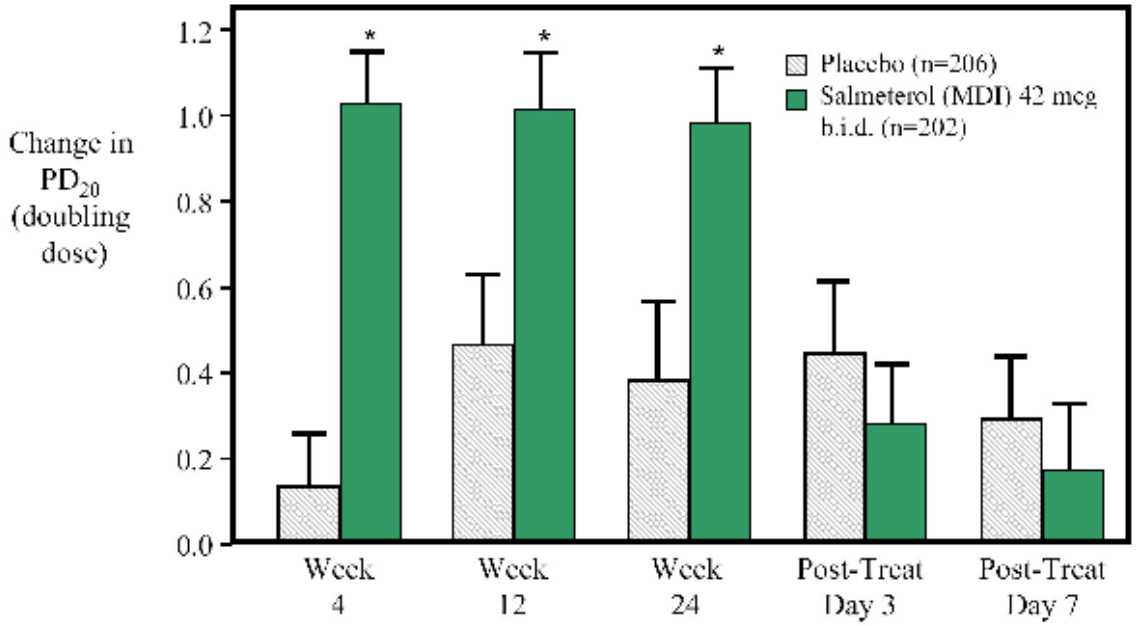
Several studies showed salmeterol exhibited a bronchoprotective effect, which was assessed using a methacholine challenge (Table 21). Cheung et al. [80] observed a high level (10-fold increase in PC_{20}) of bronchoprotection within the first 24 hours after salmeterol administration which decreased to 2-fold by week 4. In studies of longer duration, the bronchoprotective effect appears to plateau to a one to two-fold increase above baseline, similar to that provided by inhaled corticosteroids. [81] Differences in patient populations, concurrent treatments, or time of bronchoprovocation challenges in relation to dosing intervals (prior to peak response or at the end of the dosing interval) may account for variations in the bronchoprotective effects observed among studies. The clinical relevance of bronchoprovocation challenge tests has not been established.

Table 21. Bronchoprotective Effect of Salmeterol

Design, Patients	Treatment	Results
Kemp et al. (77) 52–week, DB, PL-C, R; N=352, ICS FEV_1 70-90% predicted	SAL 50 mcg dry powder inhaler BID or Placebo Methacholine PD_{20} at baseline, 4, 12, 24, 52 wks and 1-7 days post-study	PD_{20} increased and stayed at approximately 1 doubling dose with SAL vs. baseline ($P \leq 0.034$ wks 4, 24 vs. placebo). No rebound in airway hyperresponsiveness post-SAL.
Rosenthal et al. (78) 24-week, R, DB, PL-C N=408, on ALB only Mean FEV_1 ≥84% predicted	SAL 42 mcg metered dose inhaler BID or Placebo Methacholine PD_{20} at end of dosing interval wks 4, 12, 24, and 1 wk post-drug	PD_{20} increased and was higher at about one doubling dose with SAL vs. baseline ($P<0.001$ vs. placebo). No rebound airway hyperresponsiveness post-SAL. (Figure 2).
Booth et al. (82) 8-week, DB, R; N=22 (19 on ICS) Mean FEV_1 85% predicted	SAL 50 mcg metered dose inhaler BID or Placebo Methacholine PD_{20} 12 hrs post SAL at 4, 8 wks and 7-14 days post-study	SAL resulted in a 0.6 to 1.2 doubling dose greater vs. placebo ($P=0.01$). No rebound bronchial hyperresponsiveness post-SAL.
Booth et al. (83) 8 weeks; DB, PL-C, R; N=31 on ICS FEV_1 60-80% predicted	SAL 42 mcg metered dose inhaler BID or Placebo Methacholine PD_{20} during run-in, wks 4, 8 post-drug 1 hour	PD_{20} values remained at least 2 doubling doses above baseline for 8 weeks ($P<0.001$ vs. placebo).
Cheung et al. (80) 8 week, DB, R; N=24, on ALB only FEV_1 >75% predicted	SAL 50 mcg metered dose inhaler BID or Placebo Methacholine challenge (PC_{20}) 1 hour after SAL, week 4, 8	Day one, 10-fold increase in PC_{20} in SAL group. At 4 and 8 wks, a 2-fold increase in PC_{20} ($P<0.001$ vs. placebo). No rebound hyperreactivity following discontinuation of SAL.

BID=twice daily; CO=crossover; DB=double blind;ICS=inhaled corticosteroids; PC_{20}/PD_{20}=provocative cumulative methacholine conc /dose resulting in 20% decrease FEV_1; PL-C=placebo-controlled, SAL=salmeterol; SB=single blind

Figure 12. Change in Airway Hyperresponsiveness over 24 weeks[78]



*P<0.001

7. COMPARATIVE DATA

7.1 Comparison with Leukotriene Modifers for Asthma

***Serevent Diskus* versus Montelukast as add on Therapy to Inhaled Corticosteroids**

The efficacy and safety of salmeterol inhalation powder 50 mcg twice daily was compared with oral montelukast 10 mg once daily in 2 replicate, 12-week, randomized, double-blind, double-dummy, multicenter studies of patients with persistent asthma.[5] A total of 948 patients ≥15 years of age with a history of asthma for at least 6 months, a demonstrated reversibility to albuterol of ≥12%, and a mean FEV_1 = 50%-80% of predicted were enrolled. Patients were required to be symptomatic despite treatment with ICS in the 6 weeks prior to screening, with a stable ICS dose in the previous 30 days. The primary efficacy measure was morning (AM) peak expiratory flow (PEF) at endpoint.

The results showed that for AM PEF, salmeterol provided significantly greater improvements than montelukast beginning at week 1 and continuing throughout the 12-week treatment period. Similar improvements were seen with evening (PM) PEF measurements throughout the 12-week treatment period (P≤0.032, salmeterol versus montelukast for both comparisons, weeks 1-12).

In all other measures except wheezing, patients receiving salmeterol had significantly greater improvements compared to those receiving montelukast Table 22.

Table 22. Mean Change from Baseline for Symptom Scores, Rescue Albuterol Use, and Nighttime Awakening Over 12 Weeks [5]

Measurements	Salmeterol 50 mcg BID + ICS (n=452)	Montelukast 10 mg once daily + ICS (n=448)
Total rescue albuterol /day, # puffs (SE)	-1.90 (0.10)*	-1.66 (0.11)
Daytime rescue albuterol, # puffs (SE)	-1.51 (0.08)*	-1.31 (0.09)
Nighttime rescue albuterol, # puffs (SE)	-0.39 (0.04)*	-0.35 (0.04)
Percent Symptom-Free Days, % (SE)	24 (1.5)*	16 (1.3)
Percent Rescue-Free Days, % (SE)	27 (1.6)*	20 (1.4)
* p ≤0.044 versus montelukast; # = number; SE = standard error; ICS= inhaled corticosteroid; BID = twice daily		

Measurements	Salmeterol 50 mcg BID + ICS (n=452)	Montelukast 10 mg once daily + ICS (n=448)
Patient-Rated Daytime Symptom Scores		
All symptoms (SE)	-0.55 (0.04)*	-0.41 (0.04)
Wheezing (SE)	-0.47 (0.05)	-0.37 (0.04)
Shortness of breath (SE)	-0.59 (0.05)*	-0.44 (0.05)
Chest tightness (SE)	-0.60 (0.05)*	-0.42 (0.05)
Nighttime awakenings/week, # (SE)	-1.42 (0.13)*	-1.32 (0.15)
Nights/week with awakenings, # (SE)	-1.06 (0.08)*	-0.93 (0.09)
* $p \leq 0.044$ versus montelukast; # = number; SE = standard error; ICS= inhaled corticosteroid; BID = twice daily		

In surveys comparing patient satisfaction with treatment, patients receiving salmeterol had significantly higher overall satisfaction compared to those receiving montelukast (p=0.021). Patients in the salmeterol group were more likely to use study medication again compared with patients in the montelukast group (p=0.004). Both salmeterol and montelukast were well-tolerated. The frequency of adverse event reports was similar between treatment groups (7% for salmeterol and 6% for montelukast).

7.2 Comparison with Formoterol for Asthma

Adult studies

Severe Asthma

Salmeterol inhalation powder (via *Diskhaler*®) was compared with formoterol inhalation powder (device not reported) in patients with severe asthma. [84] Forty-two patients who were receiving high doses of inhaled corticosteroids (≥ 1500 mcg daily of beclomethasone dipropionate, budesonide, or fluticasone propionate) or daily oral steroid therapy (mean dose 10 mg prednisolone) and who had daily asthma symptoms and used their rescue inhaler on most days participated in the study. Their mean forced expiratory volume in one second (FEV_1) was 61.8% of predicted. The study was conducted in a randomized, placebo-controlled, crossover fashion. Dosing with formoterol was done in a double-blind fashion; only the investigators were blinded in the salmeterol arm. Patients were randomized to salmeterol 50 mcg twice daily or to formoterol 12 mcg twice daily for 4 weeks each without a washout period between treatments. The mean increase in morning peak expiratory flow rate (PEF) was significantly greater for both salmeterol (14.8 L/min) and formoterol (14.4 L/min) compared with placebo (P <0.05) with no significant difference between active treatments. In addition, there were no significant treatment differences for FEV_1, forced vital capacity, evening PEF, or daytime or evening symptom score.

Moderate to Severe Asthma

Vervloet et al. [85] conducted a 6-month, open-label, randomized, parallel-group study to compare the efficacy and safety of salmeterol inhalation powder 50 mcg twice daily (*Diskhaler*) and formoterol inhalation powder capsule 12 mcg twice daily. A total of 428 patients with moderate to severe reversible obstructive airways disease who were receiving at least 400 mcg daily of an inhaled corticosteroid (or 200 mcg daily of fluticasone propionate) participated in the study. There was no attempt to exclude patients with chronic obstructive pulmonary disease (COPD). The authors reported that salmeterol and formoterol were equally effective with no significant difference in the primary endpoint, morning pre-dose PEF during the last 7 days of treatment. There was also no difference in the use of rescue medication or the improvement in asthma symptoms. Both treatments were well tolerated; the incidence of drug-related adverse events was 13% and 9% in the formoterol and salmeterol treatment groups, respectively.

Condemi [86] conducted a randomized, open-label, parallel-group, 24-week study to compare the effects of *Serevent* and formoterol in 528 adults with moderate to severe persistent asthma (FEV_1 40%-80% predicted) who were receiving daily inhaled corticosteroids (equivalent to fluticasone propionate 200 mcg) and rescue albuterol more than 4 times per week. Patients were randomized to receive either *Serevent* 50 mcg twice daily via *Diskus* or formoterol 12 mcg twice daily. The primary endpoint was mean morning PEF measured 5 minutes after dosing by patients during weeks 1-4 of treatment. Secondary endpoints were mean pre-dose morning and evening PEF and episode-free days recorded by the patients during weeks 1-4. An episode-free day was defined as a 24-hour period in which patients had a daytime score of 0 or 1 (minimal breathing problems and no activity restrictions), a night-time symptom score of 0, and

no use of rescue albuterol. Physicians also measured the pre-dose morning PEF during weeks 1-24 of the study at scheduled office visits.

The results demonstrated that formoterol had a faster onset of action than *Serevent*, with a significantly higher (P <0.001) 5-minute post-dose morning PEF. There were no significant differences between treatment groups in the mean pre-dose morning and evening PEF during weeks 1-4 or physician-measured pre-dose morning PEF over the entire 24-week study. Patients treated with formoterol reported a significantly greater (P <0.04) number of episode-free days and significantly less (P <0.03) need for rescue albuterol than with *Serevent* during weeks 1-4. There were no significant differences between treatment groups in daytime or nighttime symptoms during weeks 1-4. The overall incidence of adverse events was comparable.

A 4-week, double-blind, randomized, crossover study by Thompson et al. [87] compared the efficacy of salmeterol 50 mcg twice daily via metered dose inhaler (MDI) and formoterol 12 mcg twice daily in 99 patients with moderate to severe asthma. Mean morning PEF was significantly greater with salmeterol (342 L/min) compared with formoterol (333 L/min) (P = 0.02). There was no significant difference between treatment groups in morning symptom scores, use of rescue medication, mean evening PEF, FEV_1, and number of symptom-free days. In addition, there was no difference in the tolerability of the two treatments. Formoterol had a significantly faster onset of effect than salmeterol with the difference between treatments appearing at three minutes and lasting up to 60 minutes.

Berger et al. [88] [89] conducted a six-month, randomized, parallel group study to compare the efficacy of salmeterol inhalation powder 50 mcg twice daily and formoterol inhalation powder 12 mcg twice daily in 528 patients with moderate to severe asthma treated with inhaled corticosteroids. Patient diaries were recorded for the first 28 days of therapy and included measurement of PEF, asthma symptoms, and rescue medication use. The primary efficacy measure, PEF at 5 minutes post-dose, was significantly greater (P = 0.0001) with formoterol compared with salmeterol. Patients treated with formoterol used significantly less (P <0.05) rescue medication than patients treated with salmeterol. There were no significant differences between treatment groups in the number of symptom-free days or in the tolerability.

Mintz et al. [90] compared the efficacy of adding formoterol inhalation powder 12 mcg twice daily, *Serevent* 50 mcg twice daily (formulation not reported), and albuterol 100 mcg as needed to inhaled corticosteroid therapy. A total of 423 patients with moderate to severe asthma ($FEV_1 \geq 50\%$ predicted) participated in the 12-week, randomized, open-label, parallel-group study. There was no difference between *Serevent* and formoterol for any of the efficacy parameters, including PEF, symptoms, awakenings, use of rescue medication, and mild and severe exacerbations. All treatments were well tolerated.

Mild to Moderate Asthma

Campbell et al. [91] conducted an 8-week, blinded, randomized, crossover study to compare *Serevent* 50 mcg twice daily via either the *Diskus* or MDI and formoterol inhalation powder 12 mcg twice daily in 469 patients with mild to moderate asthma who were receiving at least 200 mcg daily of an inhaled corticosteroid. All three treatments resulted in similar significant improvements in morning PEF. In addition, there were no significant differences between treatments for evening PEF, daytime asthma symptoms, sleep-time disturbances due to asthma, and the percentage of symptom-free days with no rescue bronchodilator use.

Nocturnal Asthma

Gabbay et al. [92] conducted a randomized, open, parallel-group study to compare the efficacy of salmeterol inhalation powder 50 mcg twice daily and formoterol inhalation powder 12 mcg twice daily in 84 patients with asthma who were stabilized on inhaled anti-inflammatory therapy. After three months of treatment, patients receiving salmeterol and formoterol had significant improvement in the number of symptom-free nights, night-time symptom scores, morning and evening PEF, and the use of rescue medication. There were no significant differences between treatments for any of the efficacy parameters.

Tolerance

Nightingale et al. [93] investigated the potential for the development of tolerance with *Serevent* inhalation powder 50 mcg twice daily via *Diskus* and formoterol inhalation powder 24 mcg twice daily. Twelve non-smoking, mild atopic asthmatics (FEV_1 >80% of predicted) participated in the double-blind,

double-dummy, randomized, crossover study. None of the patients were being treated with inhaled corticosteroids. Each treatment was given for one week. Spirometry, exhaled nitric oxide (NO), and methacholine reactivity were measured before and 12 hours after the first and last dose of each treatment. In addition, genomic DNA was isolated from blood and genotyped for $beta_2$-receptor polymorphism.

Patients receiving *Serevent* had a significantly increased FEV_1 after dose 1 (0.18 L) and the increase remained significant after one week of treatment (0.23 L).[93] Formoterol resulted in a greater initial increase in FEV_1 (0.3 L), but after one week of treatment, FEV_1 was significantly less than that of the *Serevent* group (P <0.027). *Serevent* resulted in an increased but not significant degree of bronchoprotection. A single dose of formoterol had a significant bronchoprotective effect (1.49 doubling doses) but showed tolerance after repeated dosing. After one week of treatment, both drugs resulted in similar protective effects (*Serevent*: 0.23 doubling doses; formoterol: 0.31 doubling doses). There was no relationship between $beta_2$-receptor polymorphism and tolerance to formoterol. In addition, there was no change in NO with either drug. The authors concluded that a single dose of formoterol had a greater bronchodilatory and bronchoprotective effect than *Serevent*. However, they also reported a greater tolerance with formoterol, whereas *Serevent* had a significantly greater bronchodilatory effect with a similar degree of bronchoprotection after one week of treatment.

Pediatric Studies

Capristo et al. [94] conducted an open-label, crossover study to compare the efficacy of salmeterol inhalation powder 50 mcg twice daily via *Diskhaler* and formoterol 12 mcg twice daily (formulation not reported) in 34 children with mild asthma (FEV_1 >75% of predicted). After four weeks of treatment, there were no significant differences between treatment groups in morning and evening PEF, spirometry, and symptom scores. No adverse effects were reported.

In a 12-week, randomized, parallel group study, Kamenov et al.[95] compared the efficacy of adding formoterol 12 mcg or *Serevent* 50 mcg in 150 children (ages 7-18 years) with mild/moderate asthma receiving inhaled corticosteroids. Both treatments were well tolerated and significantly improved asthma symptoms, quality of life, and albuterol use at weeks 4 and 12 compared to baseline. Compared with *Serevent*, formoterol significantly reduced albuterol use at 12 weeks (0.7 inhalations/24 hours, P = 0.04).

Safety studies in healthy subjects and patients with asthma

The biochemical and cardiovascular effects of formoterol and salmeterol were compared in 14 healthy subjects in an open, randomized, 7-way crossover study. [96] All patients received three different doses of each drug (formoterol 24 mcg, 48 mcg, and 72 mcg; salmeterol 100 mcg, 200 mcg, and 300 mcg) and placebo on separate occasions with a washout period of at least one week between treatments; all treatments were administered as an aerosol. The authors reported that the magnitude and duration of the biochemical and cardiovascular effects were similar for the three corresponding doses of formoterol and salmeterol. Only minor and/or short-lasting effects were observed on serum potassium, heart rate, blood pressure, and QTc-interval.

Guhan et al. [97] conducted a double-blind, randomized, crossover study to compare the time course for the systemic effects of three doses of salmeterol and formoterol in 16 healthy volunteers. Subjects inhaled formoterol 24, 48, and 96 mcg, salmeterol 100, 200, and 400 mcg via *Diskhaler*, or placebo on separate occasions. Heart rate, systolic and diastolic blood pressure, and plasma potassium and glucose concentrations were measured for eight hours following inhalation. The mean values for each parameter were used to plot the time course of change after each dose. Mean maximum/minimum values were used to construct dose-response curves in order to calculate the relative dose potency of salmeterol and formoterol.

Both treatments caused early dose-dependent increases in heart rate and glucose concentration and decreases in diastolic blood pressure and plasma potassium concentration. Formoterol also caused an early dose-related increase in systolic blood pressure. The effects on heart rate and blood pressure occurred more rapidly than the metabolic effects. For all parameters, except glucose response, the effects of formoterol were more rapid than salmeterol. The effects of salmeterol on heart rate were slightly more prolonged than formoterol, but the metabolic effects were apparent at eight hours after dosing with both drugs. When the maximum (or minimum for potassium and diastolic blood pressure) values were related to dose, formoterol was more potent than salmeterol for many parameters after adjusting for baseline values. The relative dose potencies for formoterol compared with salmeterol for each of the parameters up to eight hours are

illustrated (Table 23). Please note that since the daily dose of salmeterol (100 mcg) is approximately four times the corresponding daily dose of formoterol (24 mcg), a dose potency greater than 4 indicates a greater effect with formoterol than salmeterol.

Table 23. Relative Dose Potency* of Formoterol Compared to Salmeterol [97]

Time After Dosing	Heart rate	Systolic BP	Diastolic BP	QTc interval	Plasma potassium	Plasma glucose
Up to 4 hours	4.1 (3, 5.6)	12.6 (no CI)	3.3 (2.4, 4.5)	7 (2.9, 64)	5.8 (4.1, 8.6)	1.6 (0.7, 2.7)
Over 8 hour study period	2.4 (1.2, 3.8)	6 (2.1, 59)	2.1 (1.0, 3.3)	4.9 (2.0, 16)	3 (1.2, 5.7)	not calculated

*Relative dose potencies (95% confidence interval, CI) were calculated using mean maximal effects (minimum for diastolic blood pressure and plasma potassium concentrations).

BP=blood pressure;

A randomized, double-blind, double-dummy, placebo-controlled, crossover study in 18 patients with asthma (mean FEV_1 91% of predicted) compared the relative systemic effects of increasing doses of salmeterol and formoterol. [98] Patients were given increasing cumulative doses of formoterol (12, 60, 120 mcg), salmeterol inhalation powder (50, 250, 500 mcg), or placebo. Treatments were separated by a 3-12 day washout period. Before the first dose and 50 minutes after each individual dose, an ECG was recorded, serum potassium was measured, and tremor score was performed. These tests were also repeated 110 minutes after the last of the three cumulative doses.

Formoterol caused a significantly higher tremor score and a larger decrease in serum potassium than salmeterol at the highest doses. After the highest dose of each drug, 13 patients reported tremor after both formoterol and salmeterol, but the severity was significantly greater after formoterol ($P < 0.03$). The lowest serum potassium value after formoterol 120 mcg was 3.4 ± 0.1 mmol/L (range, 3.1 to 3.9 mmol/L), which was significantly lower ($P = 0.001$) than the lowest serum potassium value of 3.7 ± 0.1 mmol/L (range, 3.3 to 3.9 mmol/L) after salmeterol 500 mcg. The effects of formoterol and salmeterol on heart rate and QTc times were not significantly different. The authors noted that the greater systemic effects observed after formoterol showed that salmeterol is partial agonist versus formoterol.

7.3 Comparison with Tiotropium for COPD

Salmeterol was compared with tiotropium and placebo in two six-month, multicenter, randomized, double-blind, double-dummy, parallel group studies in patients with COPD. [99] [100] Salmeterol was administered as 50 mcg (two inhalation of 25 mcg) twice daily via metered-dose inhaler (MDI). Tiotropium was administered as 18 mcg once daily in the morning. Patients were given albuterol MDI for use as a rescue medication. Patients were permitted to continue the use of theophylline, inhaled corticosteroids, and oral steroids (up to the equivalent of prednisolone 10 mcg per day) throughout the study.

A total of 623 patients participated in Study 1 [99] and 584 in Study 2. [100] Patients were required to have an FEV_1 of less than 60% of predicted and an FEV_1/forced vital capacity (FVC) ratio of less than 70%. Patients were greater than 40 years of age with a smoking history of greater than 10 pack-years. Patients were excluded if they had a history of asthma, allergic rhinitis or atopy, an elevated total eosinophil count, or recent respiratory infection. Patients who were receiving regular daytime supplemental oxygen were excluded. Baseline patient demographics are given in Table 24.

Table 24. Baseline Patient Demographics [99] [100]

	Study 1			Study 2		
Variable	***Salmeterol* N=213**	**Tiotropium N=209**	**Placebo N=201**	***Salmeterol* N=192**	**Tiotropium N=193**	**Placebo N=199**
Age (yr)	64.6	64.5	65.6	63.5	63	63.7
Male (%)	75	74	75	75	81	77
Duration of COPD (yr)	10.4	9.2	9.7	9.4	8.9	9.9

COPD = chronic obstructive lung disease; **FEV_1** = forced expiratory volume in one second; **FVC** = forced vital capacity; **L** = liter; **N** = number of subjects; **yr** = year

	Study 1			Study 2		
Variable	***Salmeterol* N=213**	**Tiotropium N=209**	**Placebo N=201**	***Salmeterol* N=192**	**Tiotropium N=193**	**Placebo N=199**
Smoking history (pack/yr)	48	47	46	41	41	39
FEV_1 (L)	1.07	1.11	1.06	1.06	1.14	1.13
FEV_1/FVC ratio (%)	42	43.6	41.3	42.3	43.7	43.2
On theophylline (%)	23	21.5	17.4	35.9	35.2	29.6
On inhaled corticosteroids (%)	67.6	65.6	66.2	71.9	64.2	63.3
On oral corticosteroids (%)	4.7	4.8	7	—	—	—
COPD = chronic obstructive lung disease; **FEV_1** = forced expiratory volume in one second; **FVC** = forced vital capacity; **L** = liter; **N** = number of subjects; **yr** = year						

Spirometry was conducted on the first day of the study and after 2, 8, 15, and 24 weeks of treatment. In Study 1, spirometry was conducted before the morning dose and for 12 hours after the morning dose at each of these time points; in Study 2, for only 3 hours after the morning dose. Morning and evening peak flow rate and rescue albuterol use were recorded daily by patients. Dyspnea and quality of life were assessed at baseline and at 8, 16, and 24 weeks of treatment. Dyspnea was assessed using the Baseline Dyspnea Index (BDI) and the Transition Dyspnea Index (BDI). (101) Quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ). (102)

In both studies, salmeterol and tiotropium significantly improved peak and trough FEV_1 compared with placebo (Table 25). However, peak FEV_1 was significantly higher in patients receiving tiotropium compared with salmeterol in each study. There were no significant differences between salmeterol and tiotropium in morning PEF. Evening PEF, trough FEV_1, and dyspnea scores were significantly improved with tiotropium compared with salmeterol in Study 1; however, this was not replicated in Study 2. In both studies there were no significant difference in quality of life scores between salmeterol and tiotropium.

Table 25. Efficacy Results from two 6-Month Placebo-Controlled Studies (99) (100)

	Study 1			Study 2		
Outcome	**Salmeterol**	**Tiotropium**	***P*-value**	**Salmeterol**	**Tiotropium**	***P*-value**
Trough FEV_1†	85 mL*	137 mL*	0.0088	0.05 L*	0.07L*	NS
Peak FEV_1†	161 mL*	244 mL*	0.0004	0.21 L*	0.27 L*	0.0097
AM PEF‡ (L/min)	21.4*	27.3*	NS	—	—	NS
PM PEF‡ (L/min)	14.6*	32.5*	<0.05	—	—	NS
Dyspnea score (units) †	0.24	1.02*	<0.05	—	—	NS
SGRQ score (units) ‡	-3.54	-5.14*	NS	—	—	NS
Albuterol use (puffs per day)†	-1.44*	-1.45*	NS	-0.50‖§	-0.02‖§	—
P*<0.05 vs. placebo; ‖*P*-value comparison with placebo not reported †mean difference from placebo at 24 weeks; ‡mean change from baseline; §calculated from the data presented **AM = morning; **FEV_1** = forced expiratory volume in 1 second; **L** = liters; min = minutes; **NS**=nonsignificant difference; **PEF** = peak expiratory flow rate; **PM** = evening; **SGRQ** = St. George's Respiratory Questionnaire						

The most common adverse event related to tiotropium was dry mouth (10%). There were no other significant differences between treatments.

Combined Analysis of Study 1 and 2

Data from these two studies (99) (100) were combined (N=1207) to compare salmeterol and tiotropium with respect to various other health outcome endpoints including exacerbations and health resource use. (103) There were no statistically significant differences between salmeterol and tiotropium with respect to

COPD exacerbations, hospitalizations for COPD or for any cause, days in the hospital for any cause, oral steroid bursts, or unscheduled physician visits.

When data from the individual studies were combined, neither the TDI score (1.1 units vs. 0.7 units, *P*=0.17) nor the SGRQ total score was significantly different between salmeterol and tiotropium-treated patients. Combining the results from the two studies resulted in the trough FEV_1 becoming significantly higher for tiotropium compared with salmeterol (0.12 L vs. 0.09L, *P*<0.01).

Dryness of the mouth was statistically significantly higher with tiotropium (8.2%) than salmeterol (1.7%, *P*-value not reported) or placebo (2.3%, *P*-value not reported).

Study 3

In a 12-week, multi-center, randomized, double-dummy, double-blind study, salmeterol inhalation aerosol was compared with tiotropium in 653 patients with COPD. [104] Patients were ≥ 40 years of age with a smoking history of greater than 10 pack-years. Patients were required to have $FEV_1 \leq 60\%$ of predicted and $FEV_1/FVC \leq 70\%$. Patients received salmeterol 50 mcg twice daily via MDI (n=325) or tiotropium 18 mcg once daily (n=328). Patients were allowed to continue rescue albuterol, inhaled corticosteroids, theophylline, and modest doses of oral corticosteroids. Spirometry was performed at baseline and at 6 and 12 weeks of treatment. The co-primary endpoints were the average FEV_1 over 12 hours and peak FEV_1 at Week 12.

Patients had a mean age of 64 years, were 66% male, and had a mean baseline FEV_1 of 1.04 L (37.7% of predicted). More patients randomized to tiotropium compared with salmeterol were taking an inhaled corticosteroid at baseline (54.3% vs. 46.8%, respectively). At Week 12, the average 12-hour FEV_1 was 130 mL in the salmeterol group and 167 mL in the tiotropium group ($P = 0.03$). The peak FEV_1 was 216 mL in the salmeterol group and 262 mL in the tiotropium group ($P = 0.01$). Post-dose average FVC over 12 hours and peak FVC were significantly higher with tiotropium compared with salmeterol ($P < 0.05$). Rescue albuterol use decreased from baseline in both groups; however, this reduction was significantly greater with salmeterol compared with tiotropium beginning at Week 3. There was no significant difference between groups in exacerbation rate. The incidence of adverse events was comparable between treatment groups. Lower respiratory tract infections were the most commonly reported adverse event with tiotropium (12.5%) and salmeterol (17.5%). Drug-related dry mouth was reported more frequently in patients treated with tiotropium compared with salmeterol (4.9% vs. 1.2%, respectively).

Effect on Measures of Hyperinflation and Exercise Capacity

In a randomized, double-blind, crossover study of four 6-week periods, van Noord et al. [105] compared the efficacy of salmeterol inhalation aerosol 50 mcg twice daily, tiotropium 18 mcg once daily, tiotropium plus salmeterol both administered once daily, and tiotropium once daily plus salmeterol twice daily in 15 patients with COPD on measures of dynamic hyperinflation. Patients had a mean age of 66 years and a mean FEV_1 of 1.09 L and 38% of predicted. Inspiratory capacity (IC) and function residual capacity (FRC) were measured at the end of each 6-week treatment period. Three hours after the last morning dose, IC and FRC were measured at a breathing frequency of 15, 30, and 45 breaths/minute using a constant volume body plethysmograph. No significant differences were observed between salmeterol and tiotropium administered alone on inspiratory capacity. Functional residual capacity was also not significantly different between salmeterol and tiotropium at most respiratory rates (Table 26). Adverse events were not discussed.

Table 26. Effects on Measures of Dynamic Hyperinflation [105]

Parameter (L)	RR (min)	Baseline	Salmeterol BID	Tiotropium QD	Salmeterol QD + Tiotropium QD	Salmeterol BID + Tiotropium QD
IC	15	1.96	2.15	2.22	2.31*	2.34*
	30	1.69	1.77	1.91	2.02*	2.11*†
	45	1.43	1.66	1.79	1.90*	1.90*
FRC	15	4.97	4.75	4.56*	4.48*	4.38*†
	30	5.25	5.02	4.85	4.72*	4.67*
	45	5.51	5.12	4.99	4.88*	4.82*†

*$P < 0.05$ vs. salmeterol †$P < 0.05$ vs. tiotropium

BID=twice daily; **FRC**=functional residual capacity; **IC**=inspiratory capacity; **QD**=once daily; **RR**=respiratory rate

In a randomized, double-blind, crossover designed study, Webb et al. [106] compared salmeterol, tiotropium, and placebo on measures of lung hyperinflation at rest and during exercise in 12 patients with stable COPD (FEV_1 = 40% of predicted). In a crossover fashion, patients received salmeterol 50 mcg twice daily, tiotropium 18 mcg once daily, or placebo for 7-14 days with an "appropriate" washout between treatments. Two hours following dosing at the end of each treatment period, pulmonary function tests and symptom-limited cycle tests were conducted at 75% of each patient's maximal work capacity. As shown in Table 27, both salmeterol and tiotropium showed significant improvement in lung function, inspiratory capacity at rest and during exercise, functional residual capacity and exercise endurance; however, there were no significant differences between salmeterol and tiotropium in any of these outcomes.

Table 27. Effects on Measures of Lung Hyperinflation [106]

Parameter	Salmeterol	Tiotropium	Placebo
FEV_1, L	1.26*	1.26*	1.05
FRC, % predicted	163*	162*	173
IC rest, L	2.14*	2.06*	1.85
IC peak exercise, L	1.72*	1.66*	1.43
Exercise endurance, min	6.7*	7.0*	5.5

*$P < 0.05$ vs. placebo

FEV_1=forced expiratory volume in one second, **FRC**=functional residual capacity; **IC**=inspiratory capacity; **L**=liters

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